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# A CONFORMATIONAL STUDY OF VARIOUS 3- AND 4-PIPERIDINOLS

DAVID HAROLD MCMAHON

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A CONFORMATIONAL STUDY OF  
VARIOUS 3- AND 4-PIPERIDINOLS

BY

DAVID HAROLD MCMAHON

B. S., College of the Holy Cross, 1963

A THESIS

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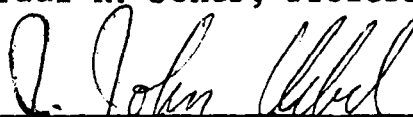
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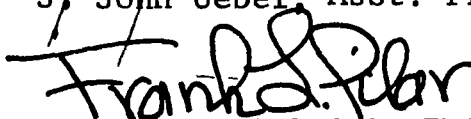
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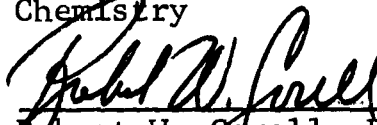
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David H. McMahon

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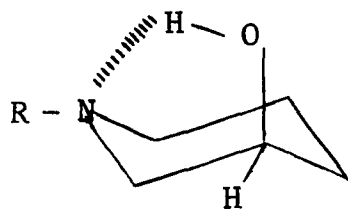
## ABSTRACT

### CONFORMATIONAL STUDY OF 3- AND 4-PIPERIDINOLS

by

DAVID H. MCMAHON

The conformational equilibria of 3-piperidinols were studied by infrared and nuclear magnetic resonance spectroscopy. The compositions of the equilibria were estimated as being 60-70% of conformer 1a from the coupling constants in the NMR<sup>1</sup>, and the intensity of the unbonded hydroxyl absorption in the infrared spectra led to an estimate of 50-60% of the conformer, 1a. These results indicated that the intramolecular hydrogen bonding of the hydroxyl group with nitrogen decreased the apparent steric requirements of the axial hydroxyl group.



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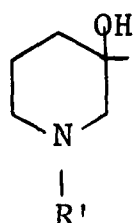


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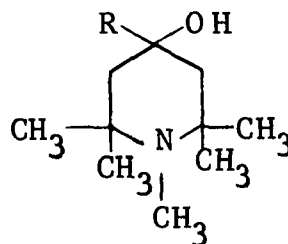
The effect of the variation in concentration, solvent and temperature on the composition of the conformational equilibrium of 3-piperidinols was studied by nmr. At higher concentrations and in hydrogen bonding solvents, intermolecular

hydrogen bonding caused a decrease in the amount of axial conformer in the equilibrium mixture.

The molar absorptivity of the unbonded hydroxyl vibration in the infrared spectrum was found to provide a method of analysis of the 3-piperidinols. Nearly all secondary and tertiary alcohols were found to give the same value for the molar absorptivity and thus could be used as models. This also allowed the estimation of the composition of the conformational equilibrium of 1,2,2,6,6-pentamethyl-4-phenyl-4-piperidinol (3).



2



3

A conformational study of the alpha isomers of the 3,5-dimethyl-2,6-diphenyl-4-piperidinols (4) by infrared spectroscopy indicated that the anomalous absorption bands at  $3652\text{ cm}^{-1}$  and  $3614\text{ cm}^{-1}$  resulted from steric interference with the hydroxyl stretching vibration, rather than from intramolecular hydrogen banding.<sup>2</sup> Thus, the spectral data can be explained on the basis of a slightly distorted chair conformer and there is no evidence which requires the postulation of boat conformations as was previously reported in the literature.<sup>3,4</sup>

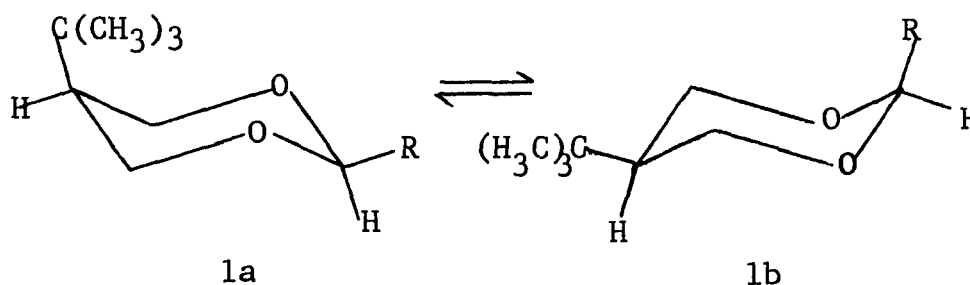
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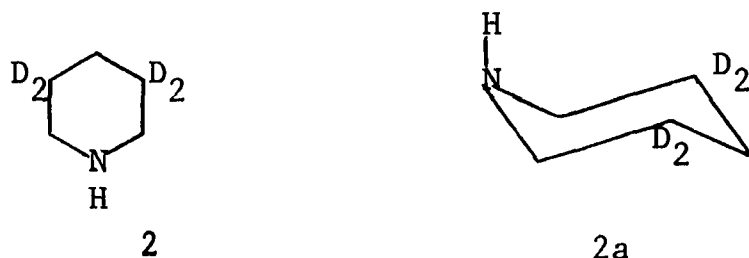
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2. R. E. Lyle and D. H. McMahon, Tetrahedron Letters, 4885 (1967).
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4. C. Y. Chen and R. J. W. LeFevre, J. Chem. Soc., 3467 (1965).

## INTRODUCTION

Extensive quantitative studies on the conformational equilibria of cyclohexane derivatives have been made.<sup>1</sup> Only preliminary measurements have been determined on the conformational equilibria of heterocyclic derivatives, however. Several aspects of the stereochemistry of heterocycles that have received attention recently are a) the determination of the "effective size" of the lone pair of electrons on the heterocyclic atom as compared with hydrogen; b) the location of the N-methyl group as axial or equatorial in piperidine or tropane derivatives; and c) the determination of whether the piperidine ring exists in a chair or boat conformation in various nitrogen heterocycles.

Recently evidence has accumulated that the lone pair on nitrogen is smaller than a bonded hydrogen<sup>2,3</sup>, although a contrary indication has also been reported by Lambert.<sup>4</sup> Eliel<sup>5</sup> reported a striking demonstration that the space requirements of a free pair on oxygen are in fact, much smaller than those of a bonded hydrogen atom. cis-2-Alkyl-5-*t*-butyl-1,3-dioxane (1) exists predominately in conformation 1a in which the *t*-butyl group is axial. Apparently this is the first instance in which a *t*-butyl group is found to assume the axial position in a six-membered ring system.



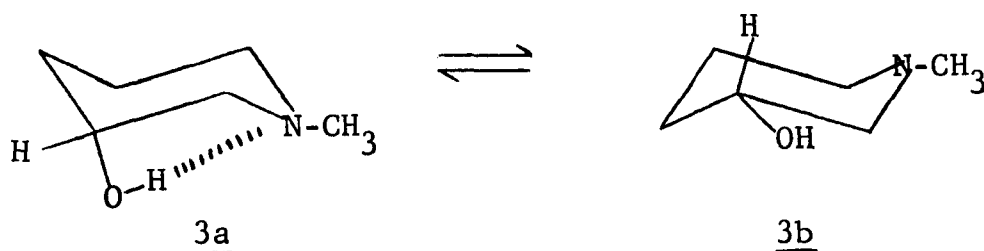


On the other hand, Lambert<sup>4</sup> reported that the space requirements of a free pair of electrons on nitrogen are larger than that of hydrogen. This conclusion was based on nuclear magnetic resonance and infrared evidence which indicated that piperidine-d<sub>4</sub>(2) existed predominately in the isomeric form with the lone pair equatorial. Lambert<sup>4</sup>, however, is in agreement with other reports<sup>2,3</sup> that the N-methyl group is equatorial in piperidine and tropane derivatives. Thus, these reports indicate that the methyl group is larger than the free pair of electrons on nitrogen.

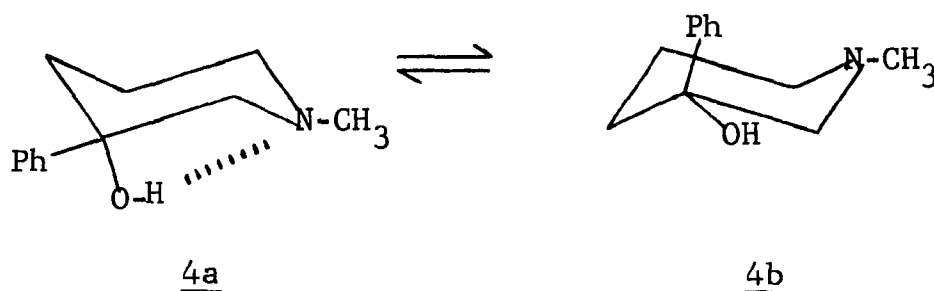
These attempts at determining the relative size of the lone pair with respect to other substituents<sup>2,3,4,5</sup>, however, have lost sight of the connection between the "size of the lone pair" and the physical data reported. The diametrically opposed conclusions obtained by Eliel<sup>5</sup> and Lambert<sup>4</sup> may both be correct, if applied to different types of experimental systems. Allinger<sup>6</sup> reported that the lone pair should not be considered explicitly at all, but rather as just a part of the nitrogen atom. Allinger<sup>6</sup> considers the concept of a "size" for the lone pair as an extremely misleading and unfortunate one, since there is no evidence which requires the "size" of the lone pair to be given explicit consideration.

The conformational questions of significance to this research concern the effect of intramolecular hydrogen bonding on the conformational free energy of two chair forms and on the equilibrium between a chair and non-chair form. The conformational equilibria of nitrogen heterocycles between two

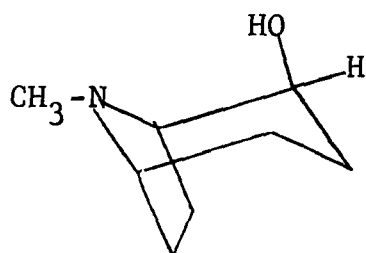
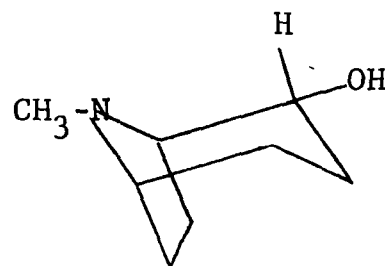
chair conformations have been investigated qualitatively for 3-piperidinols<sup>7,10</sup>, tropanols<sup>8,9</sup>, hydroxy-quinolizidines<sup>11,12</sup> and for hydroxy-indolizidines.<sup>13</sup> It follows from the geometry of the chair form that in six-membered heterocycles containing a hydroxyl group in the 3 position, only an axial hydroxyl group can form an intramolecular hydrogen bond such as in conformer 3a.



More specifically, the infrared spectrum of dl-1-methyl 3-piperidinol (3) contained two hydroxyl stretching vibrations indicative of a conformational equilibrium between a conformer having an equatorial hydroxyl (3b) and a conformer having an axial hydroxyl (3a).<sup>7</sup> Hite and coworkers<sup>7</sup> reported that the infrared spectrum of 1-methyl-3-phenyl-3-piperidinol (4) showed only a single, bonded hydroxyl-band at 3496 cm<sup>-1</sup>, indicating that 1-methyl-3-phenyl-3-piperidinol exists predominately as conformer 4a, in which the bulky phenyl group is in the equatorial position and the hydroxyl group is axial.



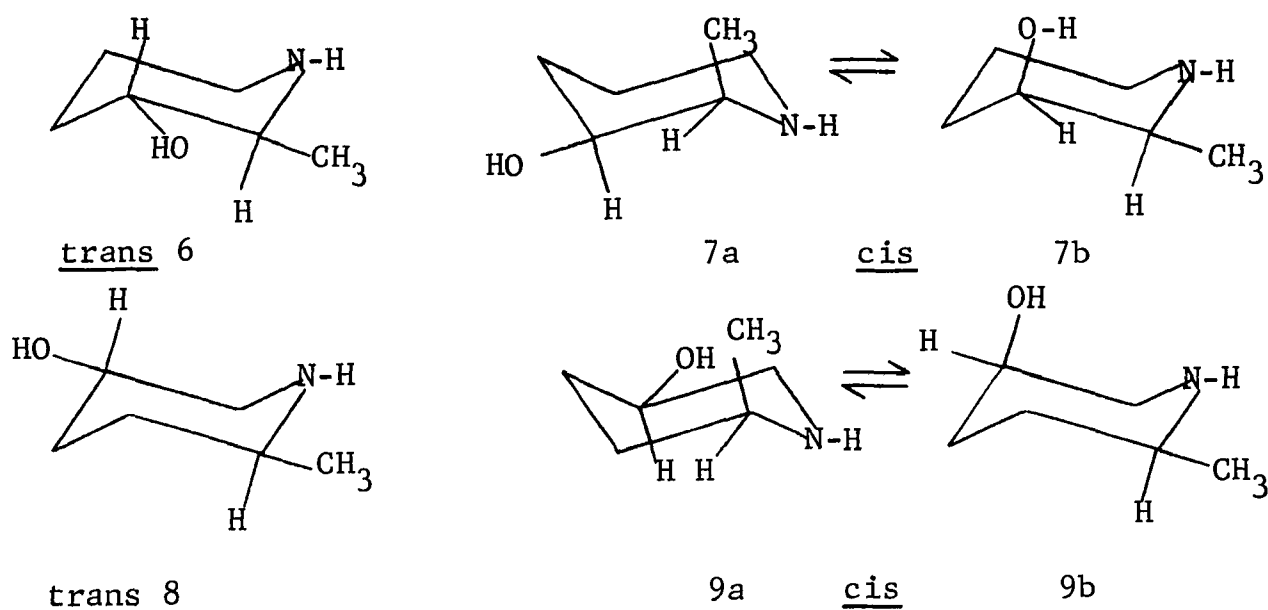
The stereochemistry of the 2-tropanols has been determined.<sup>8,9</sup> The reduction of 2-tropanone with sodium and alcohol produced the thermodynamically stable axial isomer, 2  $\beta$ -tropanol (5a), whereas the equatorial alcohol (5b) was the major product of the sterically controlled  $\text{LiAlH}_4$  reduction.<sup>8</sup> More recently House and coworkers<sup>9</sup> noted that a dilute (0.005 M) solution in carbon disulfide of 2  $\alpha$ -tropanol (5b) exhibited a single free hydroxyl stretching vibration indicating that the hydroxyl was equatorial. On the other hand, 2  $\beta$ -tropanol (5a) was reported to exhibit absorption which was attributed to an axial hydroxyl group that was intramolecularly hydrogen bonded. The stereochemistry of the 2-tropanols, therefore, was determined by the use of hydrogen bonding studies.

5a5b

Tichy<sup>10</sup> has investigated the conformational equilibria of various 3-piperidinols and the effect that substitution has on these equilibria. The spectra of trans-2-methyl-3-piperidinol (6) and trans-6-methyl-3-piperidinol (8) exhibit only free hydroxyl bands at  $3632\text{ cm}^{-1}$  and  $3624\text{ cm}^{-1}$  respectively, indicating that 6 and 8 are entirely in conformations with both substituents equatorial as shown below. By contrast the cis isomers of these compounds exhibited two hydroxyl stretching vibrations. The spectrum of cis-2-methyl-3-piperidinol (7) exhibited a free hydroxyl band at  $3632\text{ cm}^{-1}$  and a bonded peak at  $3532\text{ cm}^{-1}$ , while cis 6-methyl-3-piperidinol (9) showed a free,

unbonded hydroxyl at  $3625\text{ cm}^{-1}$  and a bonded peak at  $3532\text{ cm}^{-1}$ .

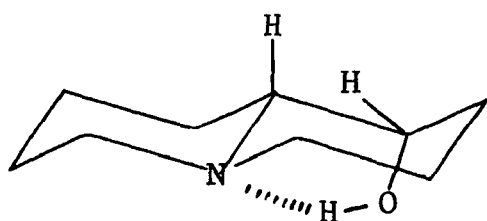
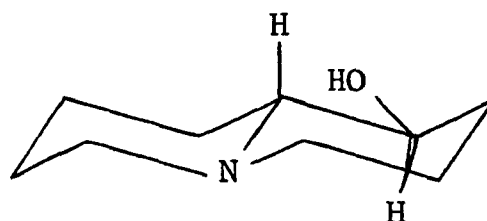
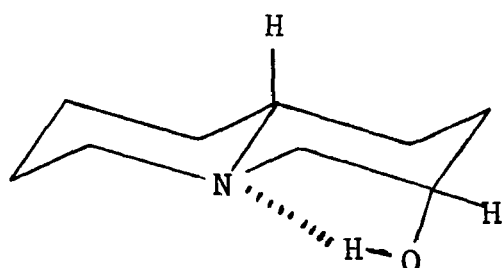
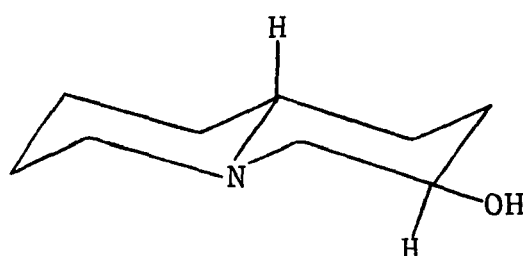
The ratio of the absorption of the area of the bonded peak ( $A_b$ ) to the area of the free peak ( $A_f$ ) in both of the cis isomers (7) and (9) was higher than that found for 3-piperidinol (34).<sup>9</sup> The increased proportion of the conformers having an axial hydroxyl (7b) and (9b) is due to the strong tendency of the methyl group to adopt the equatorial conformation.



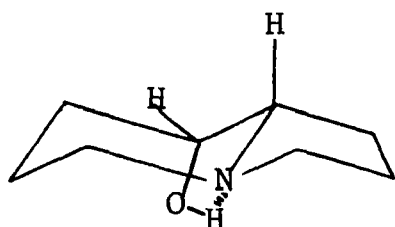
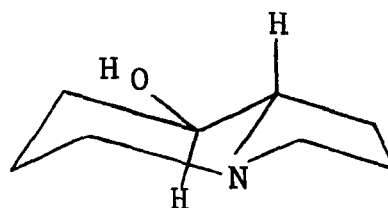
Aaron and coworkers<sup>11</sup> reported that the epimers of 1- and 3-hydroxyquinolizidine exist exclusively in one of two possible conformations. The stereochemistry of the hydroxyquinolizidines was determined by hydrogen bonding studies. In dilute carbon disulfide solution the trans epimers of 1- and 3-hydroxyquinolizidine, (11 and 13 respectively), showed the characteristic sharp absorption band of a free hydroxyl group at  $3618\text{ cm}^{-1}$  and  $3609\text{ cm}^{-1}$  respectively. On the other hand, the cis epimers of 1- and 3-hydroxyquinolizidine, (10 and 12 respectively), each exhibited in dilute carbon disulfide solution a single band, which was due to intramolecular



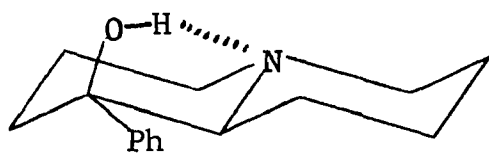
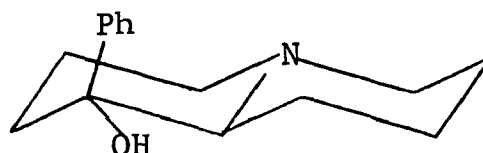
hydrogen bonding, at  $3526\text{ cm}^{-1}$  and  $3527\text{ cm}^{-1}$ , respectively.

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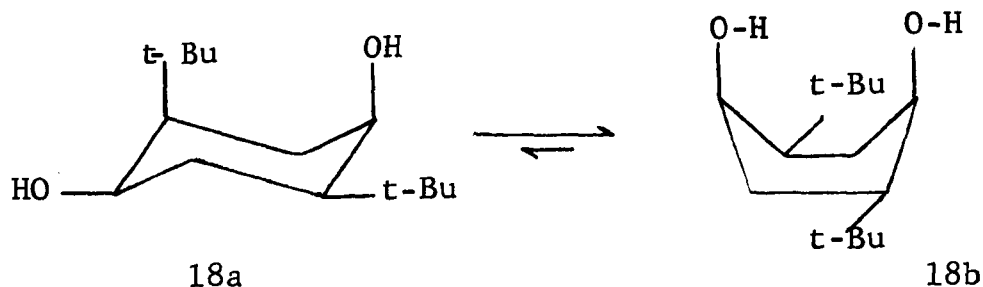
Similarly Aaron and coworkers<sup>13</sup> found in the 8-hydroxyindolizidines that the two epimers could be isolated and the stereochemistry determined by the detection of hydrogen bonding. trans-8,9-H, 8-Hydroxyindolizidine (15) exhibited a characteristic free hydroxyl band at  $3627\text{ cm}^{-1}$  in a 0.005 M solution in carbon tetrachloride, while the infrared spectrum of cis-8,9-H, 8-hydroxyindolizidine (14) exhibited a bonded hydroxyl stretching vibration at  $3522\text{ cm}^{-1}$  in a 0.007 M solution in carbon tetrachloride. This epimer 14 possesses an axial hydroxyl, regardless of the ring fusion.

1415

Sam and coworkers<sup>12</sup> reported the separation of cis- and trans-1-hydroxyl-1-phenyl quinolizidines and the determination of structure of these isomers based partially on hydrogen bonding studies. The trans isomer 17 gave a sharp free hydroxyl band at  $3620\text{ cm}^{-1}$  and an intermolecularly hydrogen bonded hydroxyl absorption at  $3430\text{ cm}^{-1}$  in a 10% chloroform solution. The cis isomer 16 gave a single broad hydroxyl absorption at  $3480\text{ cm}^{-1}$  in a 10% chloroform solution, which the authors assigned to an intramolecular hydrogen bond. This evidence is not confirmatory, however, since in 10% chloroform solutions intermolecular hydrogen bonding can be observed. If the compound is in solutions of approximately 0.005 molar or less, then intermolecular hydrogen bonding would be negligible.

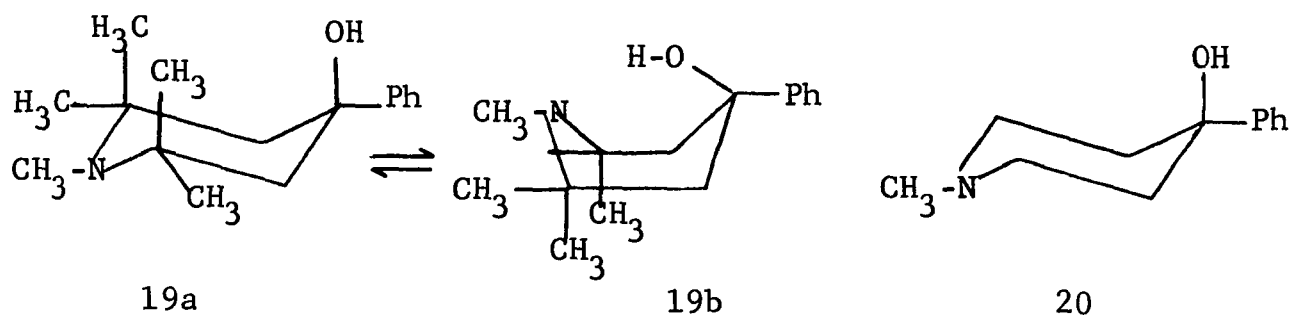
1617

Although equilibria among various chair and non-chair forms always exist, the detection of these equilibria by physical measurements is rare. With certain cyclohexane and nitrogen heterocyclic derivatives the conformational equilibria between chair and non-chair forms can be detected by hydrogen bonding studies. Intramolecular hydrogen bonds can form between cis-1,4 substituents on a cyclohexane ring if the ring adopts a non-chair conformation. One of the few examples of this was reported by Stolow and coworkers.<sup>14</sup> 2,5-Di-t-butyl-1,4-cyclohexane diol (18) exhibited an absorption band at  $3480\text{ cm}^{-1}$  in the infrared spectrum in 0.0022 molar carbon tetrachloride solution. This indicated the presence of the non-chair conformer (18b). The conformational equilibria

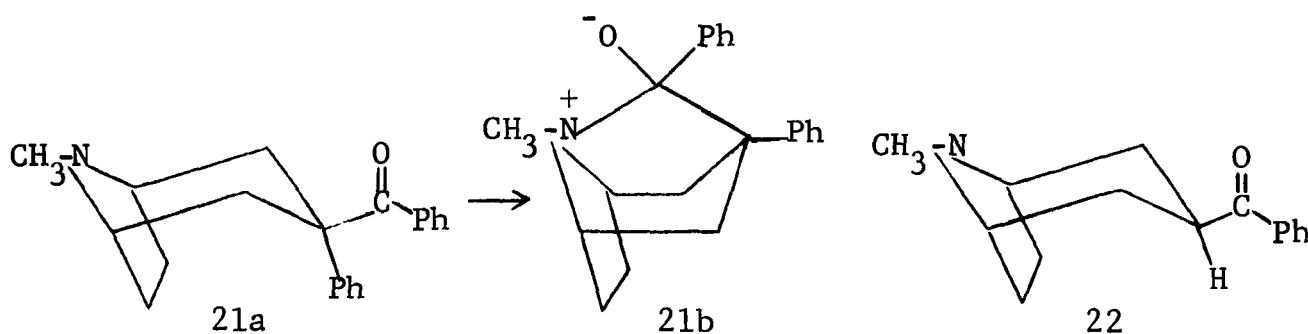


of various nitrogen heterocycles between chair and non-chair conformations have been observed in 4-piperidinols<sup>15</sup>, tropane derivatives<sup>16,17</sup>, and 3-granatanol.<sup>18,19</sup>

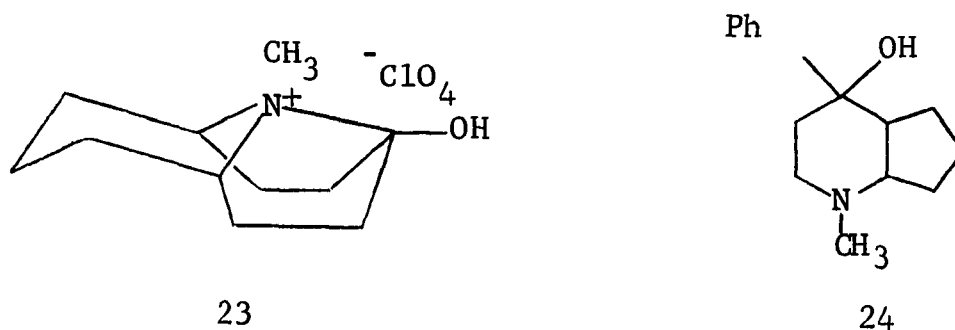
Lyle<sup>15</sup> showed that intramolecular hydrogen bonding between the hydroxyl and ring nitrogen occurred with 1,2,2,6,6-pentamethyl-4-phenyl-4-piperidinol (19), and thus it must exist in a non-chair conformation. The infrared spectrum of 1-methyl-4-phenyl-4-piperidinol (20) shows an un-bonded or  $\pi$ -bonded hydroxyl absorption. The conclusion was that in 20 the chair conformation was preferred, while in 1,2,2,6,6-pentamethyl-4-phenyl-4-piperidinol (19), the boat conformation 19b is preferred. In 19 the syn-triaxial interaction of the two methyl groups and the hydroxyl is sufficient to destabilize the chair conformation relative to the non-chair conformation (19b).



Bell and Archer<sup>16</sup> showed that phenyl 3 $\alpha$ -phenyl-3 $\beta$ -tropanyl ketone (21) exists with the piperidine ring in a non-chair conformation. The infrared and ultraviolet spectra of phenyl-3 $\beta$ -tropanyl ketone (22) were characteristic of a normal benzoyl group, while these spectra of 21 showed no benzoyl absorption in the ultraviolet, and no C=O stretching frequency in the infrared spectrum in methanol solution. The non-bonding interaction between the phenyl and the ethano bridge in phenyl-3 $\alpha$ -phenyl-3 $\beta$ -tropanyl ketone (21) appears to be sufficient to destabilize the chair conformation of the piperidine ring, causing the nitrogen to add to the carbonyl to form the amino carbinol, 21b.

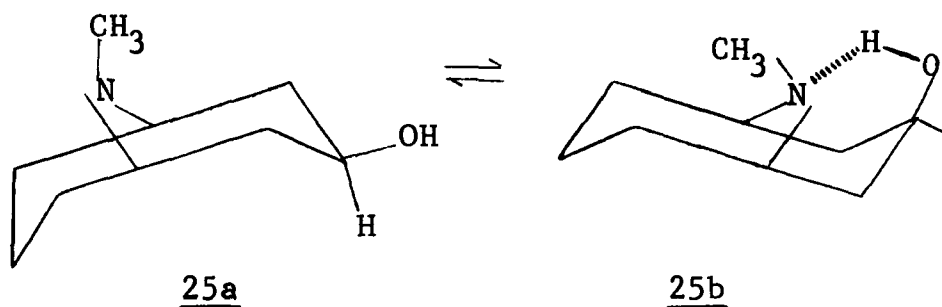


Leonard et al.<sup>17</sup> reported that the perchlorate salt of 11-methyl-11-azabicyclo [5.3.1] hendecan-4-one (23) exists in the transannular bonded form, 23, as indicated by the strong infrared absorption maximum (mull) at 3365  $\text{cm}^{-1}$  and transparency in the carbonyl region.

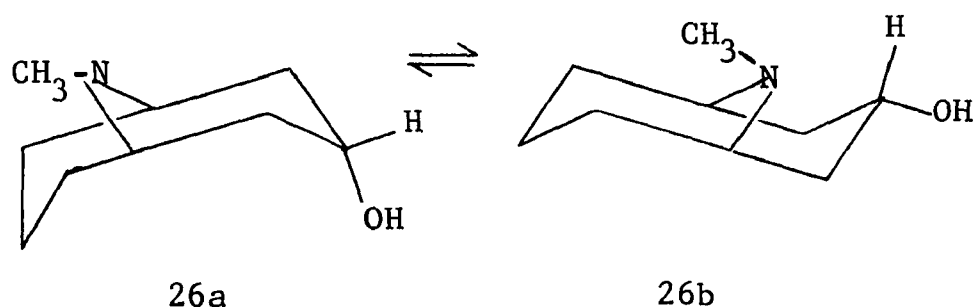


A non-chair conformation was also postulated for 24<sup>20</sup>; however, high resolution nmr and infrared spectral studies showed that the 4-piperidinol ring in tropine and pseudotropine did not exist as a non-chair conformer.<sup>9,18,21</sup> House and co-workers<sup>9</sup> have proven that the earlier report<sup>22</sup> suggesting that pseudotropine existed as a non-chair conformation was erroneous. Non-chair conformations have also been reported to exist in the isomeric 3-granatanols.<sup>18,19</sup>

The configurations of the epimeric 3-granatanols have been established by unequivocal methods<sup>23</sup>, and recently the quantitative conformational analysis of this system has been reported.<sup>18,19</sup> With respect to 3 $\beta$ -granatanol (25), the conclusions of both LeFevre<sup>18</sup> and Aaron<sup>19</sup> are in essential agreement, although they are based on slightly different considerations. LeFevre<sup>18</sup> reported that 3 $\beta$ -granatanol (25) exists as 7-8% of the chair-boat conformation 25b, while Aaron<sup>19</sup> reported that 25 exists in solution in carbon tetrachloride as an equilibrium between 89% of conformer 25a and 11% of conformer 25b. These data were based on different spectroscopic methods of analysis. LeFevre based his conclusions on the splitting pattern of the carbinol proton of 25 in the nmr spectrum, while Aaron based his results on the hydroxyl stretching vibrations of 25 in the infrared spectrum. Aaron estimated the composition of this equilibrium, which is believed to be reliable to  $\pm 5\%$ , from the integrated intensity of the free-hydroxyl stretching band relative to that of its epimeric alcohol 3 $\alpha$ -granatanol (26) [100% free OH].<sup>19</sup>



In the assignment of the conformational equilibrium of 3 $\alpha$ -granatanol (26) there is considerable disagreement. Both LeFevre and Aaron report that in the infrared spectrum of 3 $\alpha$ -granatanol (26) a characteristic free hydroxyl band exists at  $3624\text{ cm}^{-1} \pm 1\text{ cm}^{-1}$  in dilute carbon tetrachloride solution. However, LeFevre estimated the percentage contribution of the non-chair form (26b) of the 4-piperidinol to be nearly 86% in the equilibrium at 35° from the coupling constants obtained in the nmr spectrum. On the other hand, the infrared band-shape data of Aaron may be in conflict with this conclusion. Aaron<sup>19</sup> reported that the free OH band of 3 $\alpha$ -granatanol (26) is only slightly less symmetrical than that of a typical axial alcohol. This result suggests that the double chair (26a) is the preferred form for 3 $\alpha$ -granatanol (26). Aaron concluded that pending further studies of related systems, 26a should not be ruled out as the preferred conformation of 3 $\alpha$ -granatanol (26).



The conformational questions of significance to this research concern the effect of intramolecular hydrogen bonding on the conformational free energy differences between the two chair forms of 3-piperidinols and on the equilibria between chair and non-chair forms in 4-piperidinols. Analytical methods for estimating the composition of the equilibria were nuclear magnetic resonance and infrared spectroscopy. The nmr analyses

based on chemical shift differences between the axial and equatorial carbinol protons would not be reliable with these systems. The estimation of the composition from the weighted coupling constant,  $J^*$ , could be used. This, however, required the use of concentration in which intermolecular hydrogen bonding would occur. Thus an analytical method based on the infrared absorption bands for the hydroxyl stretching vibrations seemed feasible.

Using these techniques, a study of the effect of the size of the substituent at the 1-position (nitrogen) and at the 3-position on the conformational free energy change ( $-\Delta G$ ) of the 3-piperidinols was made. Similarly, a study of the effect of the size of the substituent at the 4-position on the conformational equilibria of 1,2,2,6,6-pentamethyl-4-substituted-4-piperidinols was carried out, using infrared spectral data.

The comparison of the conformational free energy change ( $-\Delta G$ ) for the 3- and 4-piperidinols with the free energy change ( $-\Delta G$ ) for cyclohexanol and 1-methyl-4-piperidinol (27) was made.<sup>24</sup> The differences in the conformational free energy change ( $-\Delta G$ ) between the 3-piperidinols and 1-methyl-4-piperidinol (27) were investigated as a measure of the effect of the intramolecular hydrogen bond. An ester of the 3-piperidinols with no hydrogen bonding possible was shown to have a conformational free energy change ( $-\Delta G$ ) similar to that of cyclohexanol and 1-methyl-4-piperidinol (27).

These studies of the conformational equilibria of the 3- and 4-piperidinols give more insight into the nature of these molecules and allow the analysis of more complex systems to be studied that contain these basic structures.

## RESULTS AND DISCUSSION

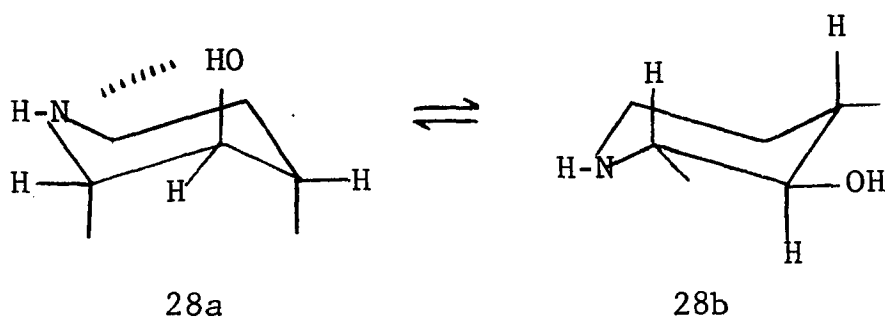
STUDY OF HYDROGEN BONDING OF 3-PIPERIDINOLS  
BY NUCLEAR MAGNETIC RESONANCE

The quantitative evaluation of importance of the intramolecular hydrogen bond of 3-piperidinols in balancing the conformational strain resulting from steric interactions of an axial hydroxyl group with the syn axial hydrogens had not been reported prior to this study. The determination of the conformational equilibrium of such a compound, and thus the conformational free energy of a piperidinol whose hydroxyl was capable of hydrogen bond formation only in the axial conformation would give an estimate of the energy of such a bond. The physical properties of several 3-piperidinols have allowed such estimates to be made and are reported here. A quantitative study of the infrared absorption band due to hydroxyl stretching vibrations and a determination of the coupling constants by the nmr provide means to estimate the composition of the conformational equilibria. The piperidinols chosen for investigation were 3-piperidinol (28), 1-methyl-3-piperidinol (3), 1-ethyl-3-piperidinol (29), 1-benzyl-3-piperidinol (30) and cis and trans, 1-methyl-4-phenyl-3-piperidinol (31 and 32, respectively). The 1-methyl-4-phenyl-3-piperidinols were prepared by routes which led to isomeric homogeneity as confirmed by gas chromatographic analysis.<sup>25,26</sup> The infrared spectral data for the hydroxyl stretching vibrations of the 3-piperidinols are summarized in Table 4 (see Figure V).

To estimate the conformational equilibria of 3-piperidinols an examination of the signals for the carbinol protons of the 3-piperidinols in the nuclear magnetic resonance spectra was undertaken. In cyclohexanol the carbinol proton gives



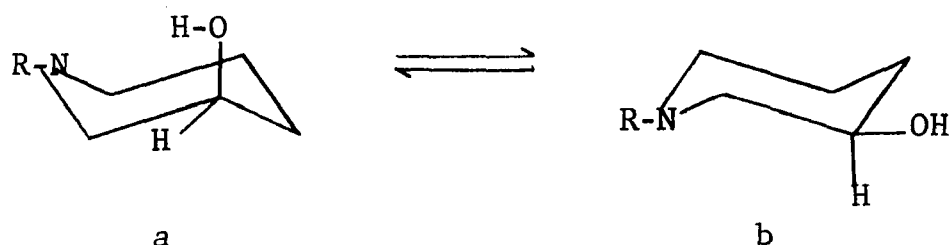
rise to a rather diffused band, and therefore the band width must be used to estimate the equilibrium composition. In most solvents the carbinol protons of the 3-piperidinols exhibit symmetrical septets from which  $J^*$  can be measured directly or determined from the band width by the method of Booth.<sup>27</sup>  $J^*$  is the weighted average coupling constant of the carbinol proton with the adjacent trans hydrogens. In the septet of the carbinol protons of the 3-piperidinols the measurement of line separations, or of the band width, combined with a knowledge of  $J_{aa}$ ,  $J_{ae}$  and  $J_{ee}$  for the piperidinol system, allowed estimation of the composition of the conformational equilibrium. From the mole fraction of the equatorial conformer, the conformational free energy change ( $-\Delta G$ ), for the conversion of an axial hydroxyl to an equatorial position, can be calculated.



To estimate the mole fraction ( $X$ ) of the conformer 28b in the equilibrium 28a  $\rightleftharpoons$  28b, the relevant coupling constants on a 3-piperidinol ring are needed. Suitable models were not available for obtaining these constants from 3-piperidinols, however, so the values obtained from 4-piperidinols and cyclohexanol were used.<sup>24</sup> Because of the similarity of the bond angles and bond lengths in cyclohexanol and piperidinol the assumption should be within the limits of analysis. A first order analysis of the resonance band for the carbinol proton in the nmr spectrum of 3-piperi-

dinol (28), a septet at  $\tau$  6.31, gave the weighted average coupling constant with the trans hydrogens ( $J^*$ ) as 8.1 Hz and 4.1 Hz for the cis hydrogens, (see Table 2 and Figure IV, Curve C). A treatment of the band width (with separation of the terminal peaks in the resonance band at  $\tau$  6.31 as 24.4 Hz) by the method of Booth<sup>27</sup> gave similar results. Using the limiting values for the coupling constants of trans diaxial ( $J_{aa}$ ) as 11.2 Hz, trans-diequatorial ( $J_{ee}$ ) as 2.5 Hz, and cis-axial equatorial ( $J_{ae}$ ) protons attached to the piperidine ring as 4.1 Hz<sup>24</sup>, the mole fraction (X) of conformer 28b having trans-diaxial hydrogens was estimated as being 0.64. This corresponds to a conformational free energy difference ( $-\Delta G^\circ$ ) of approximately 0.37 kcal/mole at 40°.

A typical set of calculations for the conversion of the  $J^*$  value to the free energy difference ( $-\Delta G$ ) is shown for 1-methyl-3-piperidinol (3) in Figure I.



- 28, R = H  
 3, R = CH<sub>3</sub>  
 29, R = -CH<sub>2</sub>CH<sub>3</sub>  
 30, R = -CH<sub>2</sub>Ph

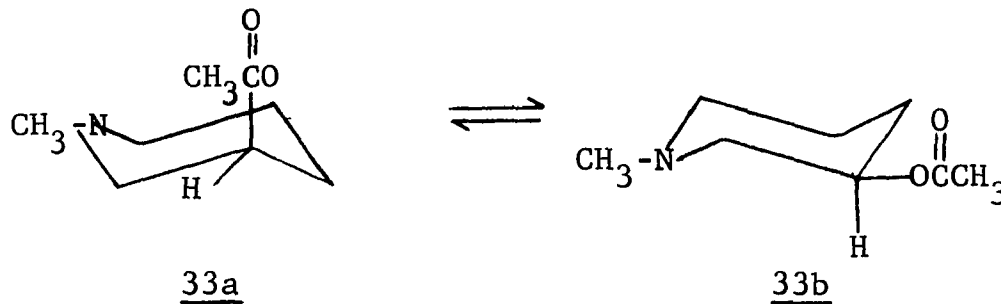
The similar analysis of the nmr spectrum of a 35% solution of 1-methyl-3-piperidinol (3), in deuteriochloroform gave a weighted coupling constant ( $J^*$ ) for the trans hydrogens with the carbinol hydrogen of 8.2 Hz (Figure II, Curve A). This value corresponds to about 65% of the conformer having the oxygen and the conformational free energy change ( $-\Delta G^\circ$ ) of about 0.39 kcal/mole. Identical results were obtained from the analysis of the nmr spectrum of a 36% solution of 1-ethyl-3-piperidinol (29) in deuteriochloroform, for the weighted coupling constant ( $J^*$ ) for the trans hydrogens with the carbinol hydrogen was also 8.2 Hz (Figure IV, Curve A).

The study of the conformational equilibrium of 1-benzyl-3-piperidinol (30) was complicated by the overlap of the resonance band of the benzyl hydrogens with the septet of the carbinol hydrogen in deuteriochloroform solution. The spacings of the lines that were not obscured were quite similar to the spacings of the same signal in the spectrum of 3 and 29, however. The conformational free-energy change for the equilibrium of 30 must also be approximately 0.4 kcal/mole.

With all the 3-piperidinols the  $-\Delta G$  is smaller by at least 0.3 kcal/mole than the  $-\Delta G^\circ$  value for 1-methyl-4-piperidinol<sup>24</sup> 27 or cyclohexanol.<sup>1b</sup> This difference results from a summation of the effects: the enthalpy of the formation of the hydrogen bond, the decrease in steric interference of the axial hydroxyl with the syn axial hydrogen in conformer 28a, any entropy effects of the hydrogen bond formation, and any dipole-dipole interactions between the carbon-oxygen and carbon-nitrogen bond.

The study of the equilibrium of 1-benzyl-3-piperidinol (30) in pyridine solution was not complicated by the overlap

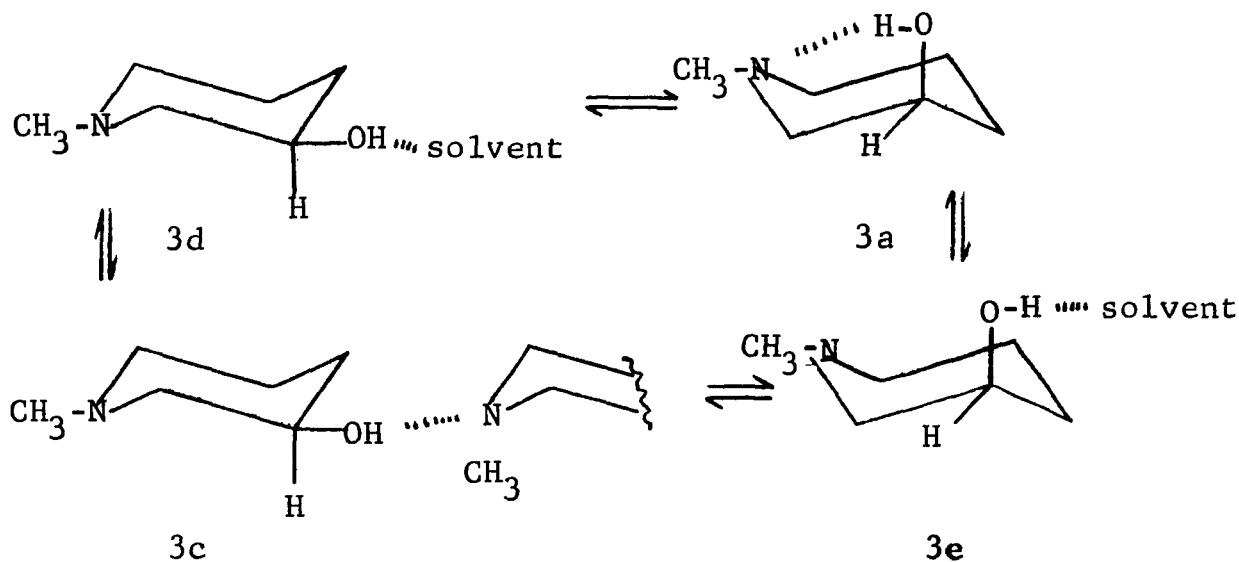
of the resonance band of the benzyl hydrogens with the septet of the carbinol proton as it had been in deuteriochloroform solution. The analysis of the nmr spectrum of a 45% solution of 1-benzyl-3-piperidinol (30) in pyridine gave a weighted coupling constant ( $J^*$ ) for the trans hydrogens with the carbinol proton of 8.8 Hz, (see Figure IV, Curve B). This value corresponds to about 73% of 30b in the equilibrium and a conformational free-energy change ( $-\Delta G^\circ$ ) of 0.61 kcal/mole (see Table 2). This is comparable to the nmr analysis of the carbinol proton of a 46% solution of 1-methyl-3-piperidinol (3) in pyridine in which the mole fraction (X) of conformer 3b was 74% (see Table 1). These compositions in pyridine are equivalent to those of the 1-methyl-4-piperidinol (27) and indicate that intramolecular hydrogen bonding is not affecting the composition of the equilibrium of 3-piperidinols in this media.



The importance of the intramolecular hydrogen bonding in decreasing the conformational free-energy difference ( $-\Delta G$ ) of 3, 28 and 29 was shown by comparison with the conformational free-energy difference ( $-\Delta G$ ) of the conformers of 1-methyl-3-acetoxypiperidine (33), in which no hydrogen bonding can occur. The weighted average coupling constant ( $J^*$ ) of 33 in deuteriochloroform was measured to be 8.8 Hz by the method of Booth<sup>27</sup> and by direct analysis of the resonance signal (see Figure III, Curve A). This value corresponds to about 73% of conformer 33b in the equilibrium and a conformational free-energy change of

0.61 kcal/mole (see Table 2). The difference between this value and the  $-\Delta G^\circ$  values of about 0.3 kcal/mole for the 3-piperidinols (3, 28 and 29) must reflect the influence of the intramolecular hydrogen bond, for the apparent steric requirements of the hydroxyl and acetoxy groups are approximately the same in the cyclohexane derivatives.<sup>1</sup> The  $-\Delta G^\circ$  value of 0.61 kcal/mole found for 1-methyl-3-acetoxy piperidine (33) is comparable to the average value of 0.7 kcal/mole reported for cyclohexyl acetate.<sup>1</sup>

The infrared spectrum of 1-methyl-3-piperidinol (3) at concentrations of  $5 \times 10^{-2}$  molar indicated that intermolecular hydrogen bonding was present, so even the most dilute nmr solution must be strongly intermolecularly hydrogen bonded. These infrared data suggest that the real equilibrium of 1-methyl-3-piperidinol (3) is not between conformer 3a, where an axial hydroxyl is bonded intramolecularly to nitrogen, and conformer 3b, where the equatorial hydroxyl is unbonded; but rather between four possible species, form 3a, form 3c, where the equatorial hydroxyl is inter molecularly bonded to the nitrogen atom of another molecule, and form 3d, in which the equatorial hydroxyl is hydrogen bonded to solvent, and form 3e, in which the axial hydroxyl is bonded to solvent.

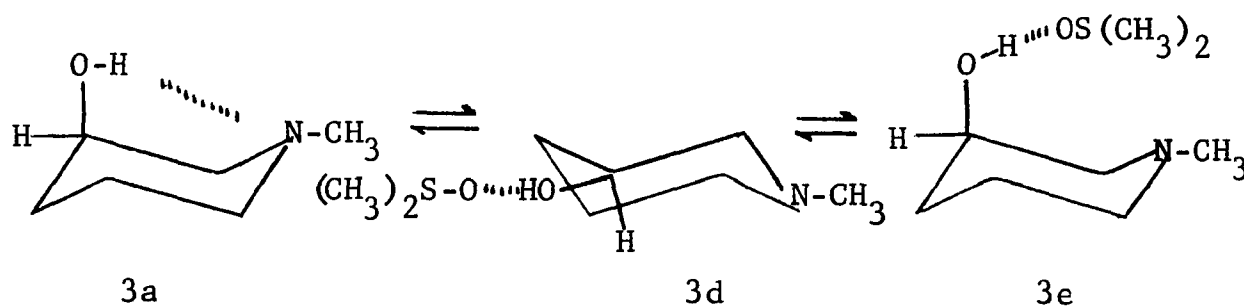


To determine the effect of intermolecular and solvent bonding on the conformational equilibria of 3-piperidinols, the variation of the conformational free-energy change ( $-\Delta G$ ) with variation of concentration, solvent, and temperature was investigated. An increase in concentration of 1-methyl-3-piperidinol (3) in deuteriochloroform would be expected to cause an increase in the amount of form 3c, which would be reflected by an increase in the equatorial conformer. The variation in solvents would effect forms 3a and 3d in the conformational equilibrium of 1-methyl-3-piperidinol (3). An increase in the basicity of the solvent would cause an increase in the importance of form 3d and again an increase in the composition of the equatorial conformer. The effect of increasing the temperature on the conformational equilibrium of 1-methyl-3-piperidinol (3) would cause an increase in the concentration of conformer 3a, in which the hydroxyl is axial.

The effect of concentration on the conformational equilibrium of 1-methyl-3-piperidinol (3) in deuteriochloroform was determined by observing the change in the average weighted coupling constant ( $J^*$ ) for the trans hydrogens with the carbinol proton. It was noted that as the concentration of 3 decreased, the weighted coupling constant ( $J^*$ ) decreased also, indicating an increase in the existence of conformer 3a, in which the hydroxyl group is axial. The analysis of the nmr spectrum of a 46.5% solution of 1-methyl-3-piperidinol (3) in deuteriochloroform solution gave a  $J^*$  of 8.6 Hz. This value corresponds to about 70% of the conformer having the oxygen substituent equatorial in the equilibrium and an apparent conformational free-energy charge ( $-\Delta G^\circ$ ) of about 0.53 kcal/mole at 41° (see Table 1). The analysis of the nmr spectrum of a less concentrated (26%) solution of 1-methyl-3-piperidinol (3) in deuteriochloroform solution gave a weighted coupling constant.

(J\*) of 8.0 Hz, corresponding to a composition of 63% of the conformer having the oxygen substituent equatorial in the equilibrium and a  $-\Delta G^\circ$  value of 0.33 kcal/mole (see Table 1). Thus, in deuteriochloroform solutions a decrease in concentration causes an increase in the amount of the conformer 3a, with the axial hydroxyl which is intramolecularly hydrogen bonded.

The effect of a hydrogen bond of the hydroxyl of 3 solvent was evident from the change in the composition of the conformational equilibrium of 1-methyl-3-piperidinol (3) with variation in solvent. The conformational equilibrium of 1-methyl-3-piperidinol (3) in dimethyl sulfoxide solution is best represented by an equilibrium predominately between conformer 3e and 3d, in which any energy gained by the enthalpy of formation of the intramolecular hydrogen bond is cancelled by the strong  $(\text{CH}_3)_2\text{S}-\text{O} \cdots \text{H}-\text{O}$  bond.



The conformational equilibrium of 1-methyl-3-piperidinol (3) in dimethyl sulfoxide has approximately the same distribution between the axial and equatorial conformers, as does cyclohexanol and 1-methyl-3-acetoxypiperidine (33) and the composition is unchanged by dilution. Deuterium oxide, a solvent strongly associated with the amino-nitrogen as well as the hydroxyl, also causes the composition of the conformational equilibrium of 1-methyl-3-piperidinol (3) to approach

that of cyclohexanol<sup>1</sup> and 1-methyl-4-piperidinol<sup>24</sup> (27). The conformational equilibrium in pyridine contained a mole fraction of the conformer with the equatorial hydroxyl only slightly greater than did the deuteriochloroform solution. Thus the basic function of 3 provided a site for intermolecular hydrogen bonding that was as effective as the weaker base pyridine present at higher concentration.

The analysis of the nmr spectrum of a 42.5% solution of 1-methyl-3-piperidinol (3) in dimethyl sulfoxide solution gave a weighted coupling constant ( $J^*$ ) for the carbinol proton of 9.4 Hz (see Figure II, Curve D). This value corresponds to 80% of conformer 3d in the equilibrium and a conformational free-energy change ( $-\Delta G^\circ$ ) of 0.85 kcal/mole at 41° (see Table 1). The analysis of the carbinol proton in the nmr spectrum of a 27% solution of 3 in dimethyl sulfoxide solution indicated that there is a difference of only 0.02 kcal/mole in the conformational free energy, 0.83 kcal/mole at 40° (see Table 1). Thus, the dimethyl sulfoxide formed a strong intermolecular bond with the hydroxyl group. The effective size of the hydroxyl group increased in dimethyl sulfoxide solution and any possibility of the axial hydroxyl group being stabilized by intramolecular hydrogen bonding was eliminated. The conformational equilibrium then would approximate that of cyclohexanol, 1-methyl-4-piperidinol (27) and 1-methyl-3-acetoxypiperidine (33). A decrease in the concentration of 3 in dimethyl sulfoxide solution would be expected to have no effect on the equilibrium and this was observed. In dimethyl sulfoxide the  $-\Delta G^\circ$  value of 1-methyl-3-piperidinol (3) was 0.83 kcal/mole, while that reported for 1-methyl-4-piperidinol (27) was 0.82 kcal/mole in dimethyl sulfoxide- $d_6$  at 40°. <sup>24</sup> Similarly a 46% solution of 3 in deuterium oxide solution had a  $-\Delta G^\circ$  value of 0.95 kcal/mole at 41° while that reported for 1-methyl-4-



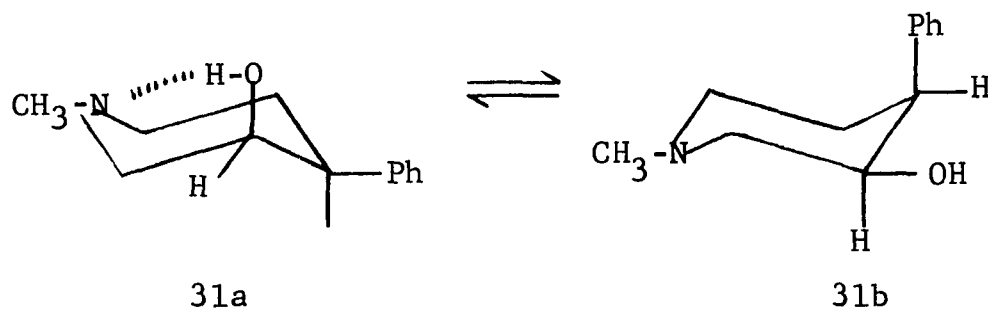
piperidinol (27) in deuterium oxide was 0.94 kcal/mole<sup>24</sup> (see Table 1). Therefore, the conformational equilibrium of 3 in dimethylsulfoxide and deuterium oxide solutions was approximately the same as that of 1-methyl-4-piperidinol (27).

The conformational equilibrium of 26% solution of 1-methyl-3-piperidinol (3) in deuteriochloroform had a  $-\Delta G^\circ$  value of 0.33 kcal/mole at 40° while LeFevre<sup>24</sup> reported that the  $-\Delta G^\circ$  value for 1-methyl-4-piperidinol (27) under similar conditions was 0.82 kcal/mole. Therefore, in deuteriochloroform, a weakly, hydrogen-bonding solvent, the  $-\Delta G^\circ$  value for 3 is not the same as that of cyclohexanol and 1-methyl-4-piperidinol (27). The difference between these values reflects the effect of the intramolecular hydrogen bond.

The effect of temperature variations on the conformational equilibrium of 1-methyl-3-piperidinol (3) was shown to be that an increase in the concentration of the less stable conformer 3a resulted on increasing the temperature. An increase in the temperature of the solution caused a decrease in the conformational free energy change ( $-\Delta G^\circ$ ) for 1-methyl-3-piperidinol (3), which had similarly been observed by LeFevre<sup>24</sup> for 1-methyl-4-piperidinol (27). A 46% solution of 3 in deuteriochloroform contained 70 mole percent of the conformer having the oxygen substituent equatorial at 40°; on heating to 80° the mole fraction decreased to 0.62 (see Table 3 and Figure III, Curve B). Similarly, LeFevre<sup>24</sup> reported that the mole fraction of 1-methyl-4-piperidinol (27) in deuteriochloroform decreased from 0.79 at 40° to 0.72 at 80°. This decrease in the mole fraction of 1-methyl-3-piperidinol (3) upon an increase in temperature was present in DMSO, D<sub>2</sub>O and pyridine, as shown in Table 3. Theoretically, the temperature could have been raised to a point at which the mole fraction of conformer 3a would be 0.50 and the conformational free

energy change ( $-\Delta G^\circ$ ) would have been equal to zero.

Using the conformational free-energy change ( $-\Delta G^\circ$ ) value of approximately 0.4 kcal/mole for the hydroxyl of a 35% solution of a 3-piperidinol in deuteriochloroform, it should be possible to estimate the conformational equilibrium for cis- and trans-1-methyl-4-phenyl-3-piperidinols (31 and 32). A value of 3.0 kcal/mole was selected as an average value for the conformational free-energy change ( $-\Delta G$ ) of a phenyl substituent<sup>1</sup>, the conformational equilibrium for 31 would be a difference between these values or about 2.6 kcal/mole corresponding to a composition of approximately 99% of conformer 31a at 37°C. The resonance band for the carbinol proton in the nmr spectrum of the cis isomer (31) showed coupling characteristics of an equatorial hydrogen. The band width of the sextet of the carbinol proton of a 27% solution of the cis isomer 31 in deuteriochloroform was 8.1 Hz (see Figure IV , Curve F). The infrared spectrum showed only a small shoulder at  $3607\text{ cm}^{-1}$  possibly due to a hydroxyl bonded to a  $\pi$  system of electrons, while the major hydroxyl stretching vibration as at  $3527\text{ cm}^{-1}$  due to intramolecular hydrogen bonding of the hydroxyl to nitrogen (see Figure VI , Curve H). All of these data are consistent with the conformational equilibrium of the cis isomer (31) containing greater than 99% of conformer 31a at 37°.



An estimation of the conformational equilibrium of trans-1-methyl-4-phenyl-3-piperidinol (32) would lead to a conformational free-energy change ( $-\Delta G^\circ$ ) of about 3.2 kcal/mole requiring approximately 99.8% of conformer 32b at 37°. The resonance signal for the carbinol proton in the nmr spectrum of a 25% solution of trans isomer (32) in deuteriochloroform was a sextet which on first order analysis gave the apparent coupling constants of  $J^*_{aa} = 9.75$  Hz and  $J_{ae} = 4.46$  Hz (see Figure IV, Curve D). Using the same limiting coupling constants applied in the conformational analysis of 1-methyl-3-piperidinol (3), the weighted average coupling constant ( $J^*$ ) of 9.75 Hz would lead to an estimation of the conformational equilibrium of the trans isomer (32) as 83 mole percent of conformer 32b and 17 mole percent of conformer 32a. The infrared spectrum of dilute solutions of the trans isomer (32) in carbon tetrachloride showed no absorption due to intramolecular hydrogen bonding of hydroxyl to nitrogen and did not support the latter estimation of the equilibrium composition. The only band present in the oxygen hydrogen stretching region was at  $3612\text{ cm}^{-1}$  indicating a weak hydrogen bond with the  $\pi$  - system of the 4 phenyl substituent (see Table 4).

To determine which of these contradictory data were being misinterpreted the nmr spectrum of trans-2-phenylcyclohexanol (34) was determined for comparison. The resonance signal for the carbinol proton in the nmr spectrum of trans-2-phenylcyclohexanol (34) in deuteriochloroform was a sextet which on first order analysis gave the weighted coupling constant ( $J^*_{aa}$ ) as 9.80 Hz; while that of the trans isomer of 1-methyl-4-phenyl-3-piperidinol (32) was 9.75 Hz (see Figure IV, Curve E). The band widths of the carbinol protons in the trans isomers of 32 and 34 were 23.9 Hz and 24.4 Hz, respec-



The conformational questions of significance to this research concern the effect of intramolecular hydrogen bonding on the conformational free-energy differences between the two chair forms of 3-piperidinols and on the equilibria between chair and non-chair forms in 4-piperidinols. Analytical methods for estimating the composition of the equilibria were nuclear magnetic resonance and infrared spectroscopy. The nmr analyses based on chemical shift differences between the axial and equatorial carbinol protons would not be reliable with these systems. The estimation of the composition from the weighted coupling constant,  $J^*$ , could be used. This, however, required the use of concentration in which intermolecular hydrogen bonding would occur. Thus an analytical method based on the infrared absorption bands for the hydroxyl stretching vibrations seemed feasible.

Using these techniques, a study of the effect of the size of the substituent at the 1-position (nitrogen) and at the 3-position on the conformational free-energy change ( $-\Delta G$ ) of the 3-piperidinols was made. Similarly, a study of the effect of the size of the substituent at the 4-position on the conformational equilibria of 1,2,2,6,6-pentamethyl-4-substituted-4-piperidinols was carried out using infrared spectral data.

The comparison of the conformational free-energy change ( $-\Delta G$ ) for the 3- and 4-piperidinols with the free-energy change ( $-\Delta G$ ) for cyclohexanol and 1-methyl-4-piperidinol (27) was made.<sup>24</sup> The differences in the conformational free-energy ( $-\Delta G$ ) between the 3-piperidinols and 1-methyl-4-piperidinol (27) was investigated as a measure of the effect of the intramolecular hydrogen bond. An ester of the 3-piperidinols with no hydrogen bonding possible was shown to have a conformational free-energy change ( $-\Delta G$ ) similar to that of cyclohexanol and 1-methyl-4-

piperidinol (27).

These studies of the conformational equilibria of the 3- and 4-piperidinols give more insight into the nature of these molecules and allow the analysis of more complex systems to be studied that contain these basic structures.

Table 1

Changes in the coupling of the carbinol hydrogen with the adjacent trans hydrogen which occur on varying the concentration of 1-methyl-3-piperidinol (3) in several solvents

<u>Solvent</u>	<u>Conc. Wt. %</u>	<u>J* (Hz)</u>	<u>Mole percentage</u>	<u>-ΔG</u>
DCCl <sub>3</sub>	46.5	8.6	0.70	0.53 <sup>a</sup> kcal/mole
	35	8.2	0.65	0.39 <sup>b</sup>
	26	8.0	0.63	0.33 <sup>b</sup>
Pyridine	46	8.95	0.74	0.66 <sup>a</sup>
D <sub>2</sub> O	46.5	9.6	0.82	0.95 <sup>a</sup>
DMSO	42.5	9.4	0.80	0.85 <sup>a</sup>
	36	9.3	0.78	0.79 <sup>b</sup>
	27	9.35	0.79	0.83 <sup>b</sup>

1-ethyl-3-piperidinol

DCCl <sub>3</sub>	36	8.2	0.65	0.39 <sup>a</sup>
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1-benzyl-3-piperidinol

Pyridine	45	8.5	0.69	0.49 <sup>c</sup>
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<sup>a</sup> Measured at 41°    <sup>b</sup> Measured at 40°    <sup>c</sup> Measured at 37°

Table 2

Conformational Analysis of Various 3-Piperidinols by  
the Splitting of the 3-Proton in the nmr

<u>3-Piperidinol</u>	<u>Solvent</u>	<u>Concen- tration %</u>	<u>Chemical Shift <math>\tau</math></u>	<u>Band Width Hz</u>	<u>J* Hz</u>	<u>Mole Percentage of equatorial hydroxyl</u>	<u><math>-\Delta G^{40^\circ}</math></u>
1-H (28)	DCCl <sub>3</sub>	30	6.36	---	8.0	.635	.34
	Pyridine	30	6.31	24.4	8.1	.645	.37
1-CH <sub>3</sub> (3)	DCCl <sub>3</sub>	35	6.24	24.1	8.2	.65	.39
	Pyridine	46			8.95	.74	.66
1-CH <sub>2</sub> CH <sub>3</sub> (29)	DCCl <sub>3</sub>	36	6.26	23.9	8.2	.65	.39
1-CH <sub>2</sub> Ph (30)	Pyridine	45	6.25	25.4	8.8	.73	.61
1-CH <sub>3</sub> (33)	CCl <sub>4</sub>		5.23	25.5	8.8	.73	.61
3-Acetyl	Neat		5.42	26.0	8.9	.74	.64





## FIGURE I

Calculation of the Mole Fraction and  $-\Delta G^\circ$  of a 35% Solution of 1-Methyl-3-piperidinol (3) at  $37^\circ$  in Deuteriochloroform from the NMR Coupling Constants

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$J^*$  is measured directly from the nmr spectrum  
(Figure II, Curve A)

$$J^* = J_{aa}X + (1-X) J_{ee}$$

$X$  = mole fraction of 3b

If  $J^* = 8.2$  Hz and the values<sup>24</sup> of  $J_{aa} = 11.2$  Hz

$$J_{ee} = 2.5 \text{ Hz}$$

Then

$$8.2 = 11.2X + (1-X) 2.5$$

$$X = 0.65 \text{ mole fraction of } \underline{3b}$$

Determination of the Equilibrium Constant and  $-\Delta G^\circ$

$$K_{eq} = \frac{X}{(1-X)} = \frac{0.65}{1-0.65} = 1.85$$

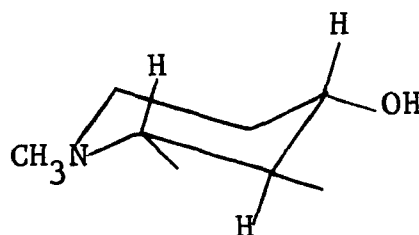
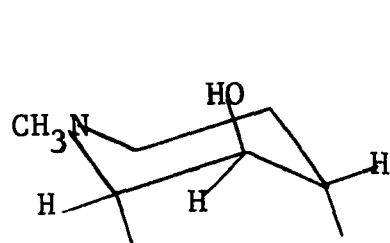
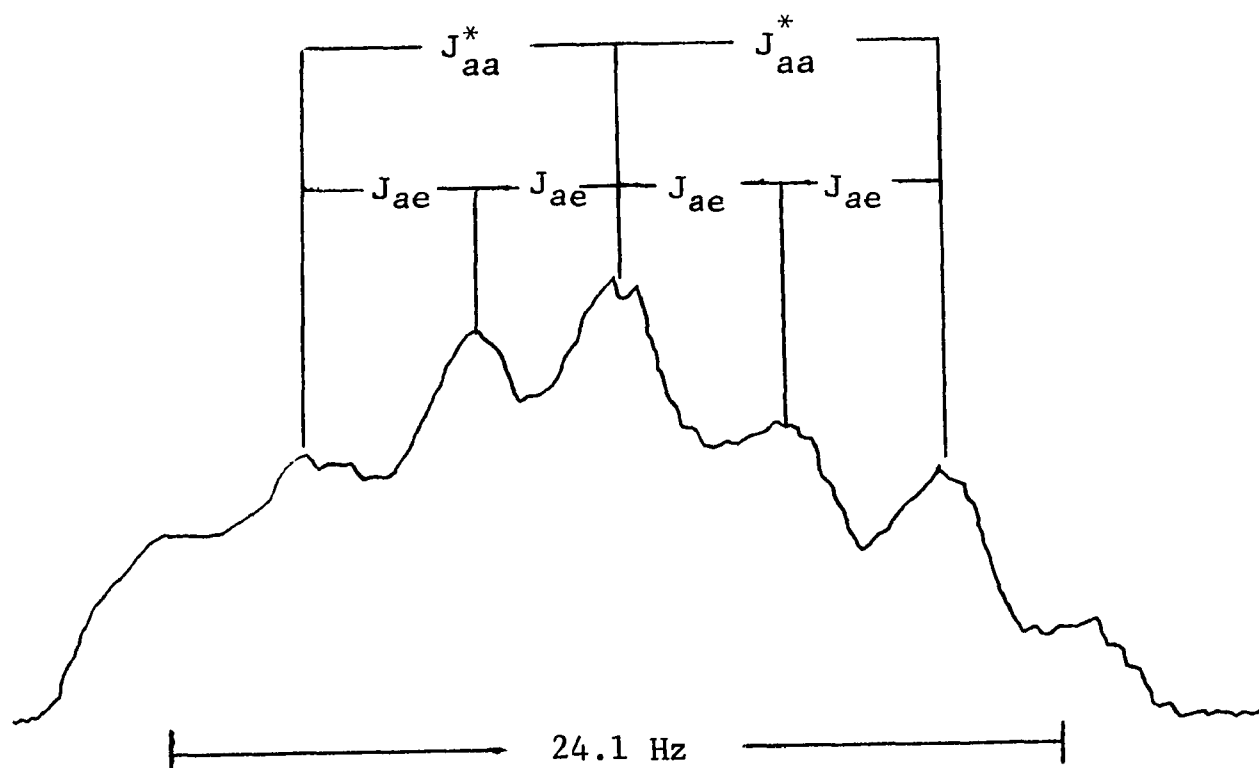
$$-\Delta G^\circ = RT \ln K_{eq}$$

$$-\Delta G^\circ = 1.99 \times 310 \times 2.303 (\log 1.85)$$

$$-\Delta G^\circ = 0.39 \text{ kcal/mole}$$

FIGURE II

Carbinol Protons of N-Methyl-3-piperidinol (3)  
with Sweep Width of 100 Hz at 41°



35%  $\text{DCCl}_3$   
 $J^* = 8.2 \text{ Hz}$   
Curve A

FIGURE II

Carbinol Protons of N-Methyl-3-piperidinol (3)  
with Sweep Width of 100 Hz at 41°

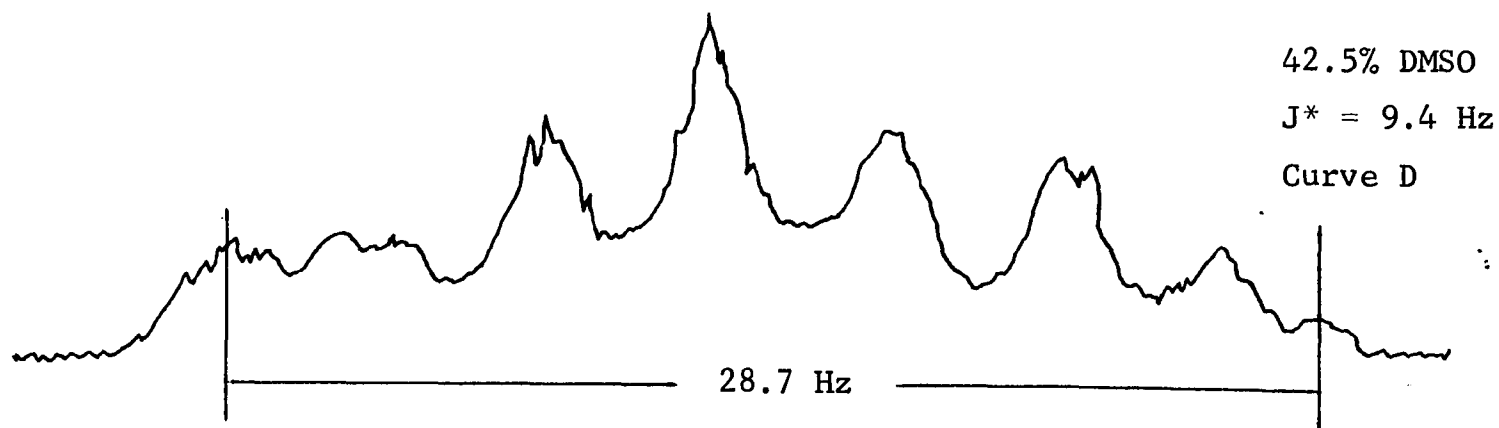
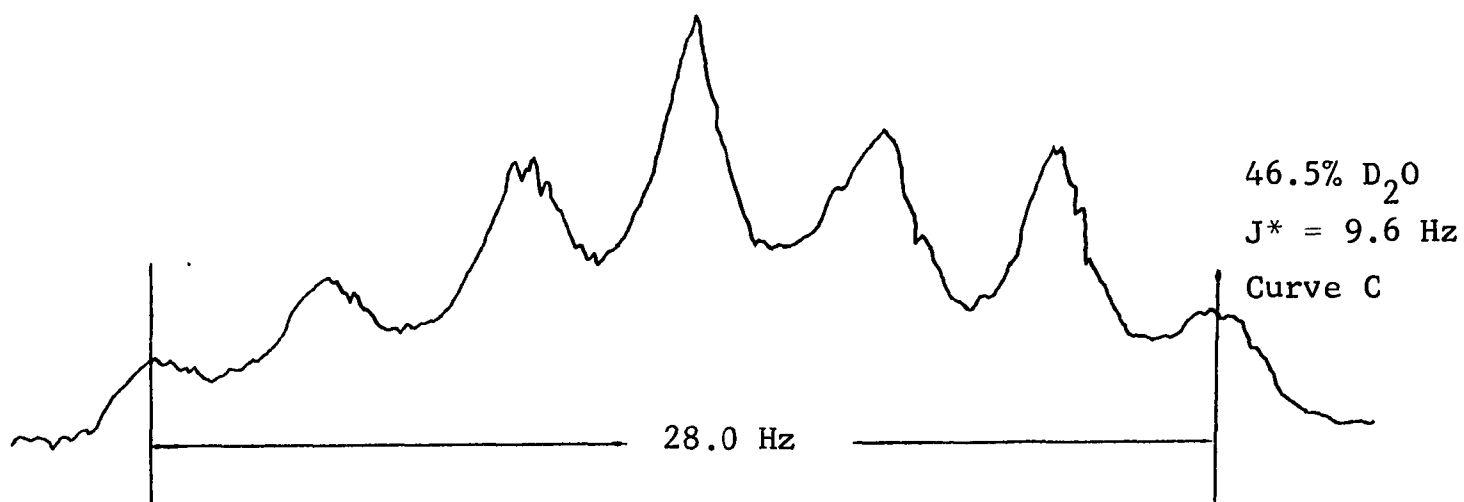
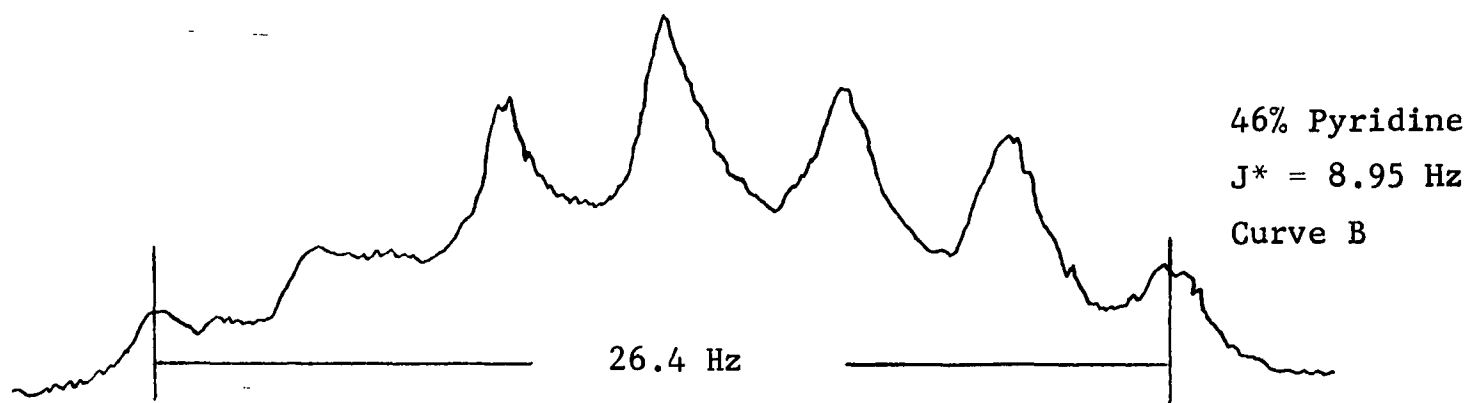
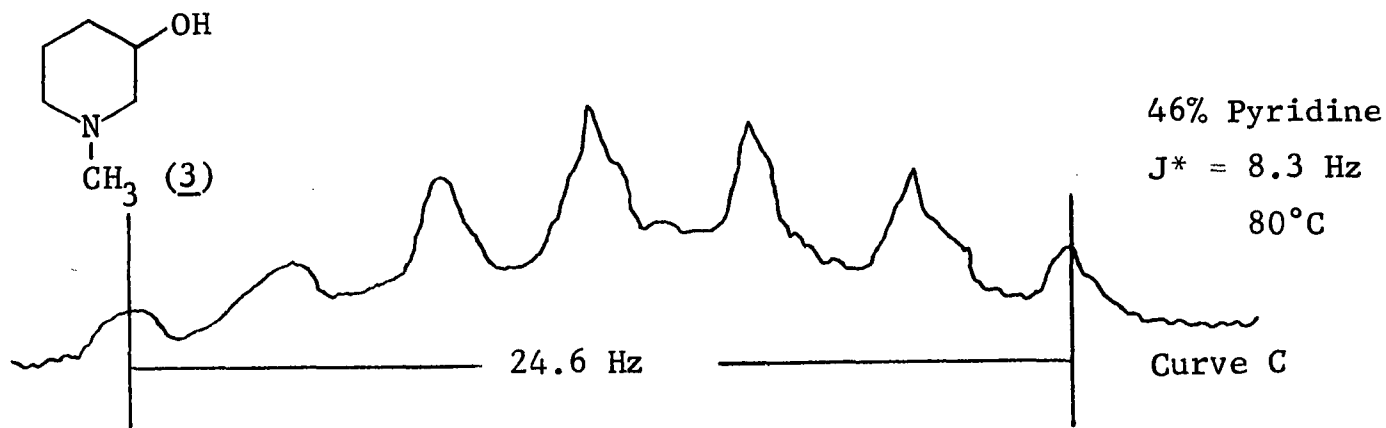
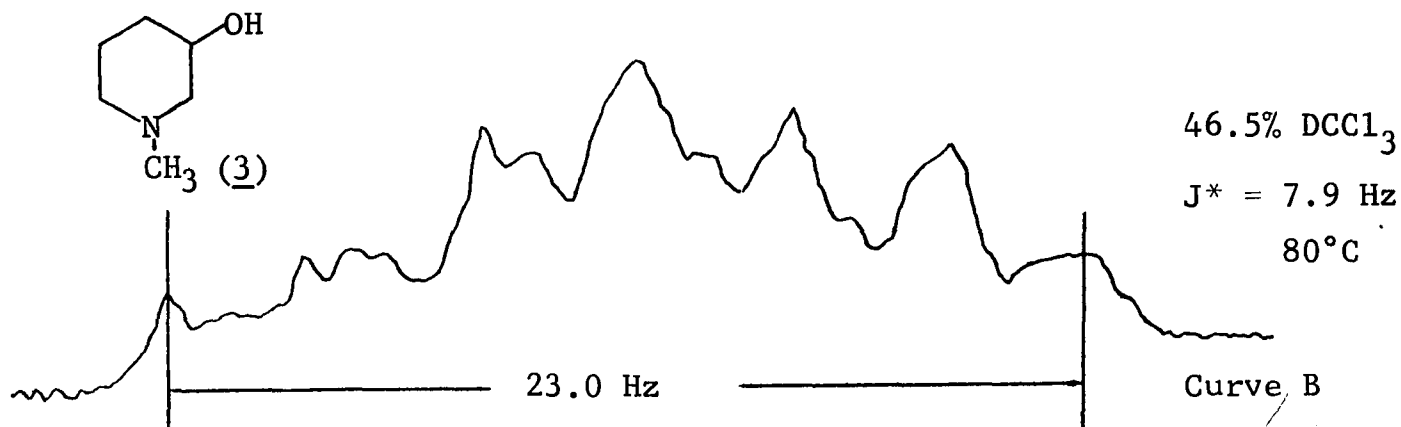
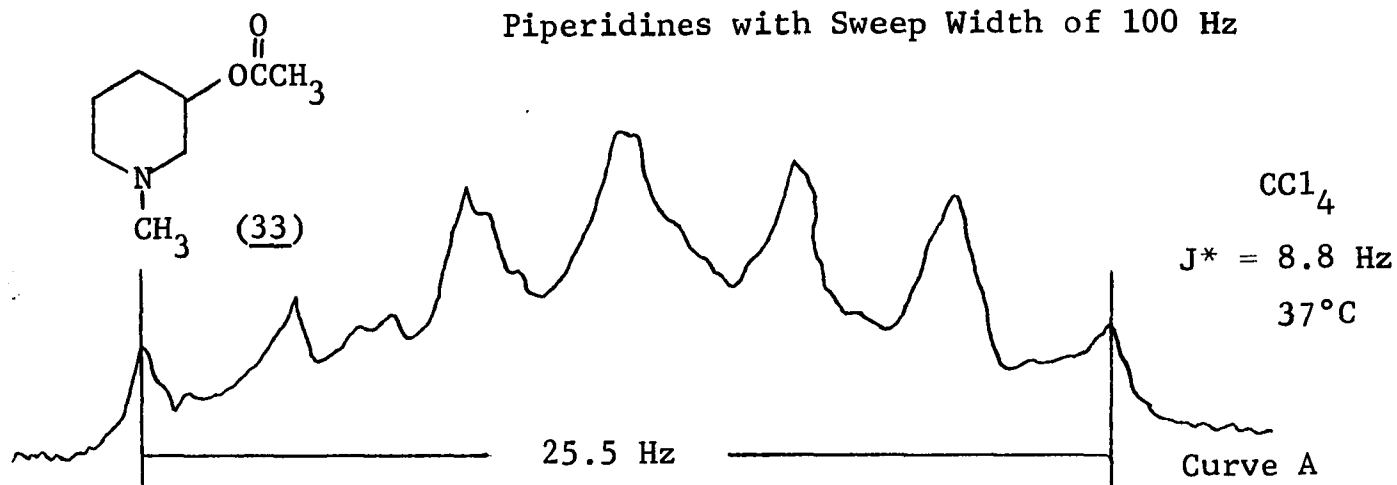


FIGURE III

Carbinol Protons of 3-Substituted  
Piperidines with Sweep Width of 100 Hz



Carbinol Protons of Various 3-Piperidinols  
with Sweep Width of 100 Hz at 37°C

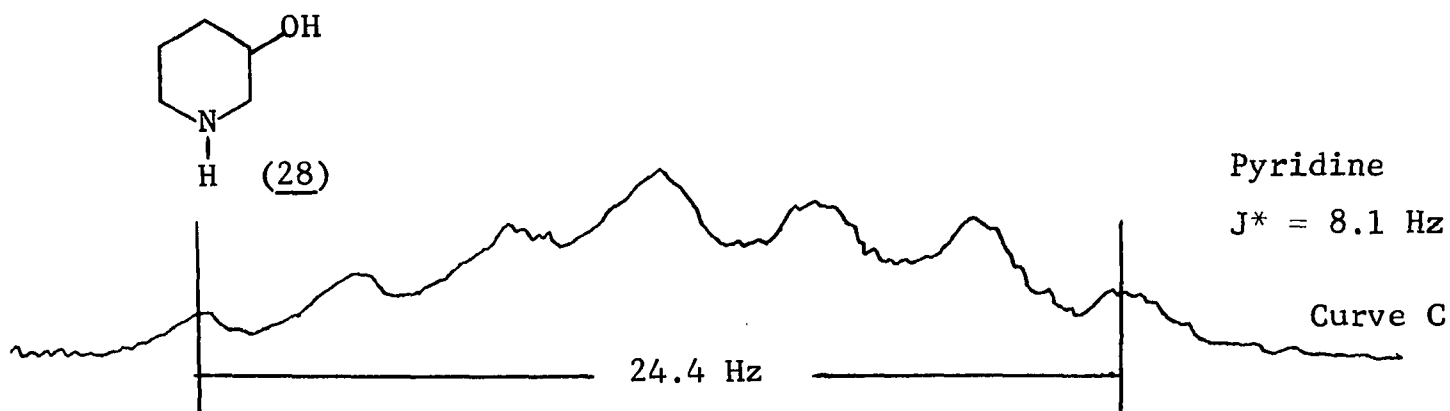
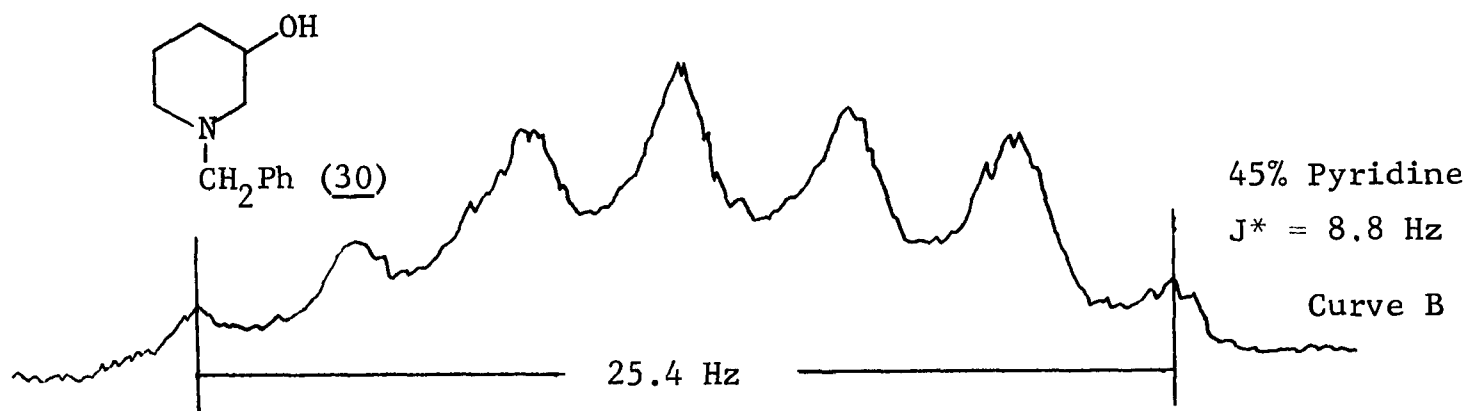
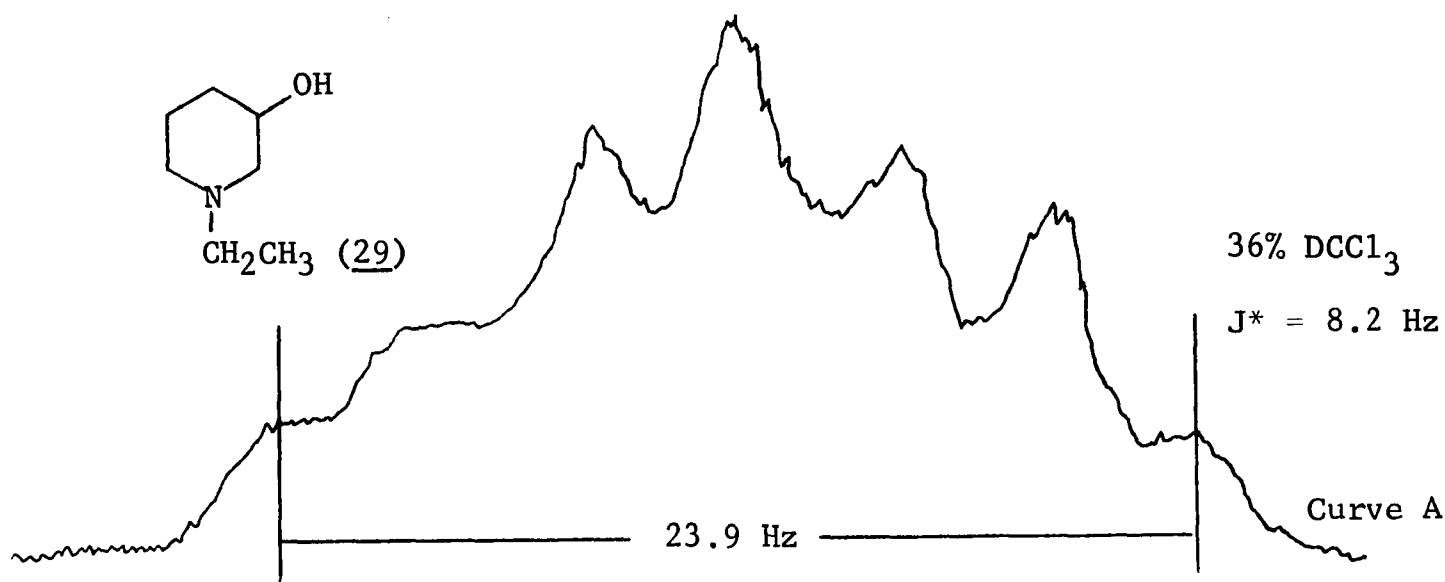
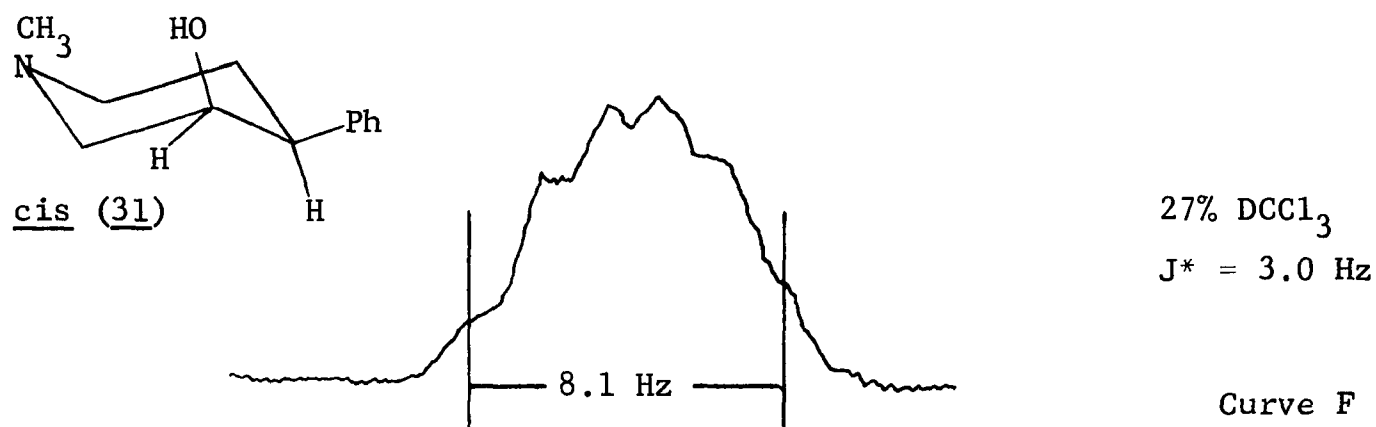
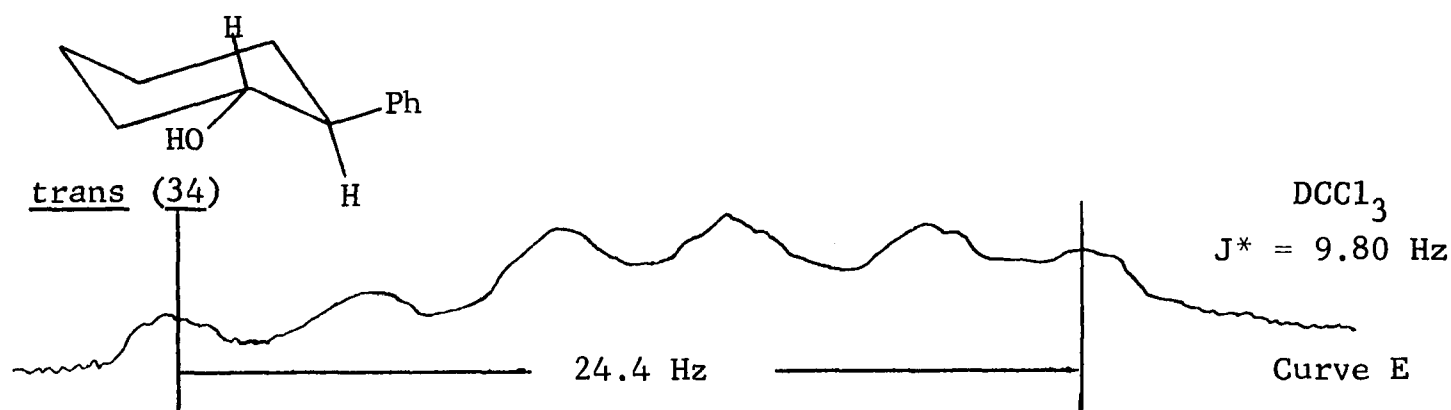
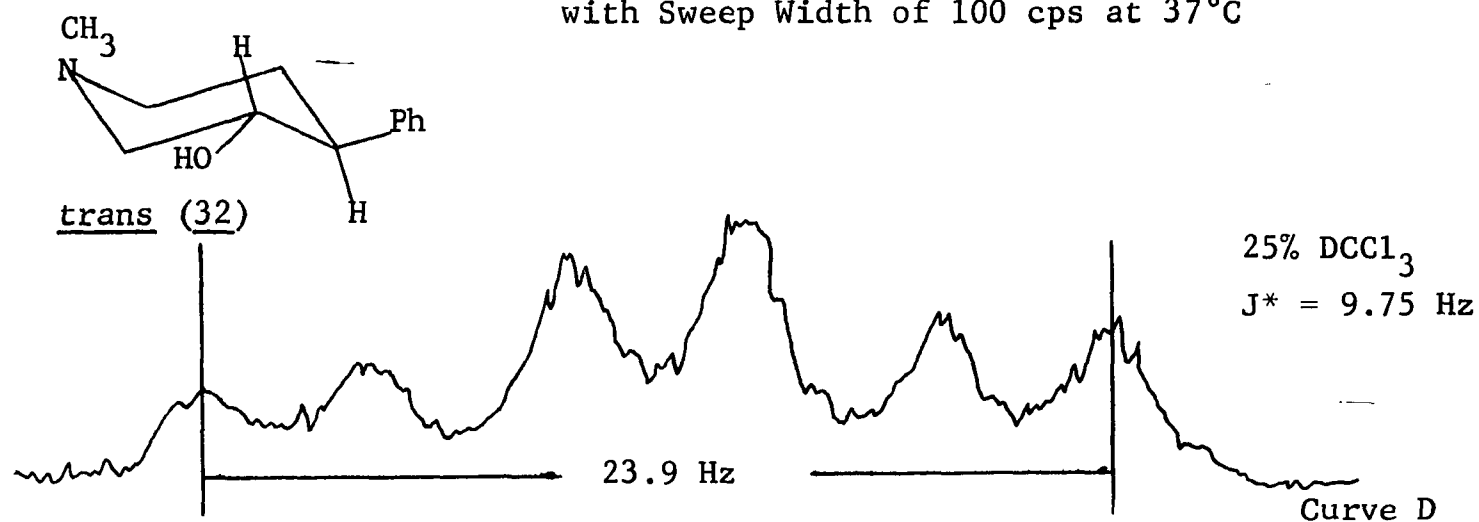


FIGURE IV

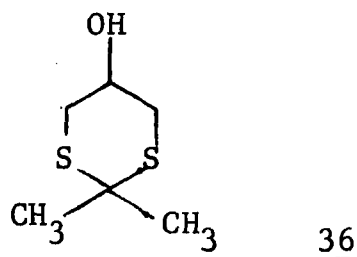
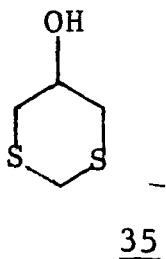
Carbinol Protons of 3-Piperidinols  
with Sweep Width of 100 cps at 37°C



## STUDY OF HYDROGEN BONDING BY INFRARED SPECTROSCOPY

The existence of intramolecular hydrogen bonds in a variety of piperidinol derivatives has been well established.<sup>7,10</sup> The 3-piperidinol derivatives are particularly important in showing this type of absorption. Although the 3-piperidinols exhibit two absorption bands in the  $3400\text{--}3650\text{ cm}^{-1}$  region due to bonded and unbonded hydroxyls, the relative intensities of the two bands have shown limited use as a quantitative estimate of the conformers present.<sup>1</sup>

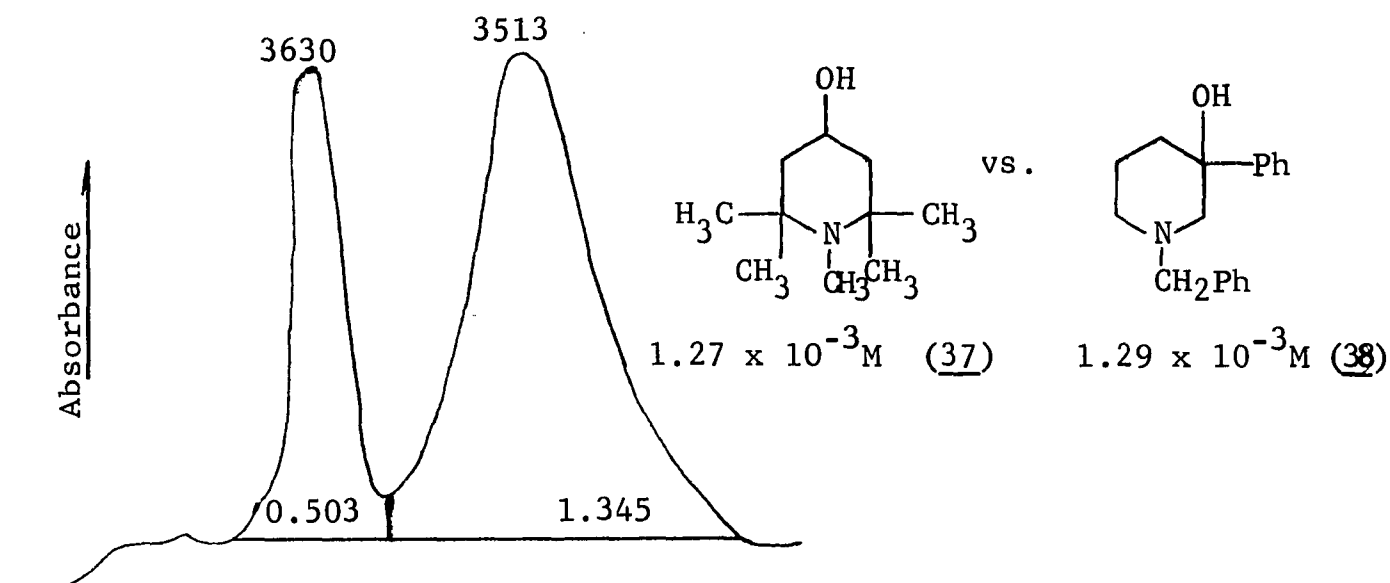
Luttringhaus and coworkers<sup>28</sup> reported that the molar absorptivity of the bonded and unbonded hydroxyl absorption bands in the infrared spectra of 5-hydroxy-1,3-dithian (35) are essentially equivalent. Similar conclusions were made by Abraham and Thomas<sup>29</sup> in the study of the conformational equilibrium of 2,2-dimethyl-5-hydroxy-1,3-dithian (36). In contrast, Tichy<sup>20</sup> reported that the bonded hydroxyl bands have an increased intrinsic integrated intensity, a greater half band width, and a higher molar absorptivity than the unbonded hydroxyl bands. Tichy<sup>20</sup> concluded that it was not possible to evaluate with any accuracy the relative concentrations of associated and non-associated conformers just from the ratio of the integrated intensities of the bonded and unbonded hydroxyl bands. To use the infrared absorption bands for the quantitative estimation of the two conformers therefore required a reconsideration of this question.





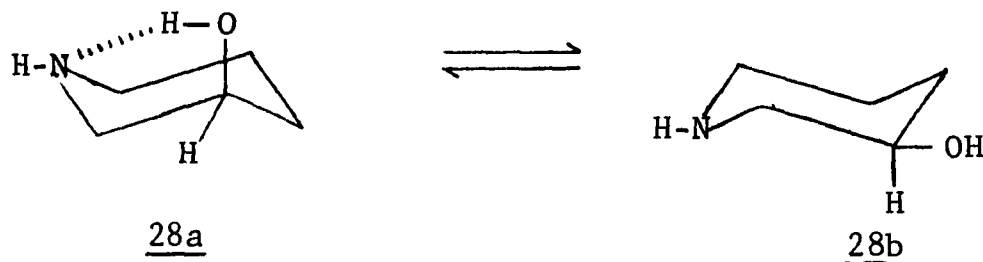
A solution was prepared which contained 49.6 mole percentage of 1,2,2,6,6-pentamethyl-4-piperidinol (37) and 50.4 mole percentage of 1-benzyl-3-phenyl-3-piperidinol (38). The infrared spectrum of 37 only showed absorption due to an unbonded hydroxyl stretching vibration at  $3630\text{ cm}^{-1}$ <sup>38</sup>, while the infrared spectrum of 38 exhibited absorption at  $3513\text{ cm}^{-1}$  due only to the form in which the hydroxyl is bonded to nitrogen. The integrated absorptivity of the absorption bands in the mixture were 0.503 for 37 and 1.345 for 38. Thus the molar absorptivities for the bonded and unbonded hydroxyl groups were not equal, which was in agreement with the results of Tichy.<sup>20</sup>

#### Infrared Spectra of Mixture of Piperidinols



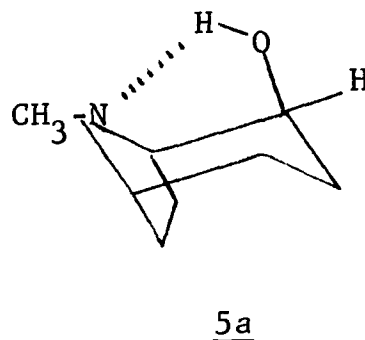
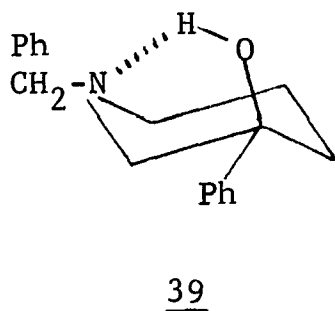
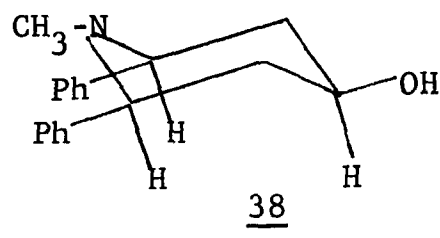
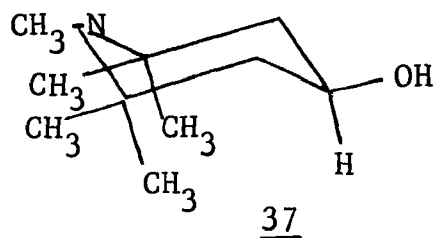
A number of piperidinols have been found which exhibit a single absorption band in the infrared hydroxyl stretching region due either to intramolecularly hydrogen-bonded or unbonded hydroxyls (see Table 4). Using such compounds as standards, it seemed likely that a calibration curve could be

developed which would allow the determination of the ratio of the molar concentrations of the bonded and unbonded hydroxyls in a mixture, be it a mixture of conformers (28a and 28b) or different compounds.



The infrared spectrum of 1,2,2,6,6-pentamethyl-4-piperidinol (37) showed a single unbonded hydroxyl band<sup>38</sup>, and  $\alpha$ -1-methyl-2,6-diphenyl-4-piperidinol (39) similarly showed an unbonded hydroxyl absorption at  $3628\text{ cm}^{-1}$ . These compounds were chosen as standards for the unbonded, equatorial hydroxyl. On the other hand, 1-benzyl-3-phenyl-3-piperidinol (38) showed a single absorption band, which was due to a hydroxyl intramolecularly bonded to nitrogen. 2  $\beta$ -Tropanol (5a) showed a single absorption band at  $3478\text{ cm}^{-1}$  which was assigned as the stretching vibration of an axial hydroxyl that was intramolecularly bonded to nitrogen.<sup>9</sup> These compounds were chosen as models for the conformers 28a in which the hydroxyl is axial and hydrogen bonded to nitrogen. The mixtures of 37 with 38 and of 39 with 5a were prepared with the total concentration approximately 0.0025 molar. The infrared spectra of these solutions were measured in the region of hydroxyl stretching absorption and the integrated intensities of the two absorption bands were determined (see Table 5). The plot of the composition of the mixture vs the ratio of the areas in absorbance of the unbonded peak ( $A_f$ ) to the bonded peak ( $A_b$ ) gave a curved line. The plot obtained using the mixture of 37 and 38 was nearly identical with that obtained

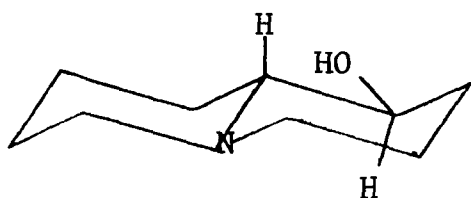
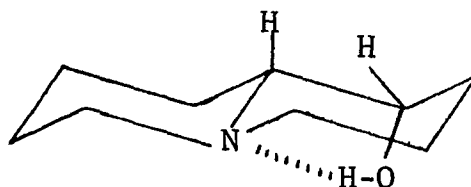
from the mixture of 39 and 5a. The calibration curve obtained by plotting the composition of the mixture vs the ratio of the area of the unbonded peak ( $A_f$ ) to the area of the bonded peak ( $A_b$ ) as used to estimate the composition of the conformational equilibria of the 3-piperidinols. From these data the conformational free energy difference ( $\Delta G$ ) of the 3-piperidinols can be calculated. It was later shown that this method was not correct since the  $A_b$  varied with the nature of the structure.



During the course of this investigation, Coke<sup>30</sup> reported that a similar method for estimating the conformational equilibrium of 1-methyl-3-piperidinol (3) was under consideration. His study used trans-1,10-hydrogen 1-quinolizidinol (11) as a standard for the unbonded hydroxyl, and cis-1,10-hydrogen 1-quinolizidinol (10) which showed a single band at  $3540\text{ cm}^{-1}$  as a model for the conformer 3a, in which the hydroxyl is axial.<sup>11</sup> Coke based his estimates of the composition of the equilibrium of 1-methyl-3-piperidinol (3) on the analysis of

the bonded absorption, 10 as standard, since the absorption due to traces of water sometimes overlapped the absorption band of the free hydroxyl absorption and since the resolution of the bonded and unbonded hydroxyl absorption bands varied.

These two difficulties were much less serious for the bonded hydroxyl absorptions. Coke used a Perkin-Elmer Model 421 infrared grating spectrophotometer to obtain the spectra plotted in transmittance, which were then converted to absorbance by the method of White.<sup>31</sup> Using the peak height, in absorbance, of the OH stretching absorption of cis-1,10-hydrogen 1-quinolizidinol (10) as standard, Coke estimated the conformational equilibrium of 1-methyl-3-piperidinol (3) in dilute carbon tetrachloride solution at room temperature as having 82% of conformer 3a in which the hydroxyl was axial. These results were not consistent with the results obtained from our plot of the composition of the mixture vs  $A_f/A_b$ , in which the estimate of the composition of the equilibrium of 1-methyl-3-piperidinol (3) was 51% of axial conformer 3a. This inconsistency led us to reevaluate the analytical techniques employed.

1110

In our preliminary investigation the infrared spectra had been determined in transmittance with a Perkin-Elmer Model 337 spectrophotometer equipped with a scale expansion apparatus. In the spectra obtained by this method, however, it was found that the hydroxyl absorption due to traces of water overlapped the absorption band of the free hydroxyl (see Figure VI). It

was also found that the scale expansion apparatus did not give areas of the hydroxyl absorptions that were consistent on separate determinations using the same solution. The infrared spectra determined in absorbance with a Beckman Model 12 infrared, grating spectrophotometer did not have these limitations. It was found that the hydroxyl absorption due to traces of water was completely resolved from the unbonded hydroxyl absorption and using cells of 10 cm path length eliminated the need for the scale expansion apparatus. The areas of the peaks for the bonded and unbonded hydroxyls in absorbance were found to be consistent on repeated determinations of the spectra using the same solution. Thus the Beckman Model 12 was used for all subsequent studies, rather than the Perkin-Elmer Model 337 spectrophotometer.

The infrared absorption spectra of the 3-piperidinols were determined as carbon tetrachloride solutions of less than 0.0025 molar concentration (see Figure 5). The model compounds containing either the bonded or unbonded hydroxyl groups were determined under similar conditions. The area of the absorption band of the model compound was plotted against its molar concentration. It was found that the plot for 1-benzyl-3-phenyl-3-piperidinol (38) gave a straight line, whose molar absorptivity was approximately  $10.5 \times 10^3$ . The molar absorptivity is defined as the ratio of the integrated absorptivity to the molar concentration of the species times the cell path length (cm.). Similarly, the plots for 2  $\beta$ -tropanol (5a) and cis-1,10-hydrogen 1-quinolizidinol (10) were determined. The molar absorptivity of 5a and 10 were found to be  $8.5 \times 10^3$  and  $5.8 \times 10^3$ , respectively (see Table 6). The fact that the molar absorptivity varied for the three standard compounds, in which the hydroxyl is axial, indicated that the various plots of molar concentration vs area of bonded

absorption would yield three different straight lines (see Figure VII). The existence of three different straight lines for the different bonded standards, in which the hydroxyl is axial, led us to the conclusion that the choice of this absorption band for an analytical standard would be a poor one for determining quantitatively the concentrations of the conformers of 3-piperidinols.

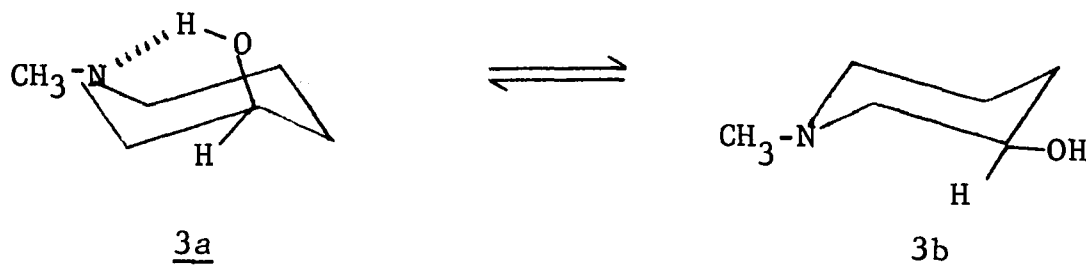
A similar treatment of the data obtained with the model compounds having an unbonded hydroxyl group gave molar absorptivities which were constant. The model compounds which had unbonded hydroxyl groups were 1,2,2,6,6-pentamethyl-4-piperidinol (37), trans-1,10-hydrogen 1-quinolizidinol (11),  $\beta$ -3,5-dimethyl-2,6-diphenyl-4-piperidinol (40b), 1,4-dimethyl-2,6-diphenyl-4-piperidinol (41) and cholesterol (see Table 7). The molar absorptivity did not appear to depend greatly upon the groups to which the hydroxyls were attached. Piperidinols and carbocyclic systems such as cholesterol gave similar molar absorptivities, as did tertiary alcohols such as 1,4-dimethyl-2,6-diphenyl-4-piperidinol (41). The average molar absorptivities taken as standard for the unbonded hydroxyl group was  $3.74 \times 10^3$ . The absorptivity of the axial hydroxyl of  $\beta$ -3,5-dimethyl-2,6-diphenyl-4-piperidinol (40b) was comparable to that of the other piperidinols, but the absorptivity of the equatorial hydroxyl group of 3,5-dimethyl-2,6-diphenyl-4-piperidinol (40a) was not the same. If the area of the band of 40a at higher frequency ( $3652 \text{ cm}^{-1}$ ) only was considered, the molar absorptivity was  $3.64 \times 10^3$ . Therefore with all compounds containing an unbonded hydroxyl that were examined, except 40a, the absorptivity of the hydroxyl stretching absorptions were comparable. This is exemplified by the plot of the molar concentration of the model compounds having unbonded hydroxyls vs the area, in absorbance, of the infrared

band of the unbonded hydroxyl. The points described a single straight line (see Figure VIII). Aaron and Rader<sup>19</sup> similarly have reported that there was little difference in the integrated band areas of the unbonded secondary hydroxyl absorption which they examined. This was especially true for members of epimeric pairs. Cole and coworkers<sup>32</sup> are in agreement with Aaron and Rader that no significant differences have been found for the band area of unbonded hydroxyl epimers.

The significance of these results is the constancy of the absorption of the unbonded hydroxyl, which indicated that any compound having an unbonded secondary or tertiary hydroxyl from isopropanol to trans-1,10-hydrogen 1-quinolizidinol (11) could have been used as a model compound. The extension of these results to the estimation of the hydroxyl concentration is far reaching. The unbonded absorption can be used to estimate the composition of conformational equilibria of not only the 3- and 4-piperidinols, but also of any other compounds having an unbonded hydroxyl conformer present.

The concentration of the conformer containing the unbonded, equatorial hydroxyl in the conformational equilibria of 3-piperidinols can be estimated directly from the plot of area of the band for the unbonded hydroxyl vs the molar concentration or by calculation using the average molar absorptivity of  $3.74 \times 10^3$ . The mole percentage of the conformer 3b of 1-methyl-3-piperidinol (3) having the unbonded hydroxyl was found as the ratio of the concentration of 3b with the total concentration of 1-methyl-3-piperidinol (3) times 100 (see equation 1). The molar concentration of the conformer 3b with the equatorial unbonded hydroxyl is equal to the integrated absorptivity of the unbonded hydroxyl divided by the molar absorptivity times the cell path length (cm.). For example, the integrated absorptivity of the band for the

unbonded hydroxyl of 1-methyl-3-piperidinol (3) is 0.536 which corresponds to a composition of 57% of conformer 3b.



Molar absorptivity  $\frac{\text{Integrated Absorptivity (in}^2 \cdot 0.1 \text{ abs. unit)}}{(\text{abs. unit/mole} \times \text{cm}) \times \text{cell path length (cm)}} =$   
molar conc.

$$\frac{0.536}{3.74 \times 10^3 \times 10} = .00143$$

$$1 \text{ in.} = 0.1 \text{ abs. unit}$$

$$\frac{\text{molar conc.}}{\text{total conc.}} \times 100 = \% \text{ unbonded conformer}$$

$$\frac{.00143}{.00250} \times 100 = 57\%$$

#### Equation 1

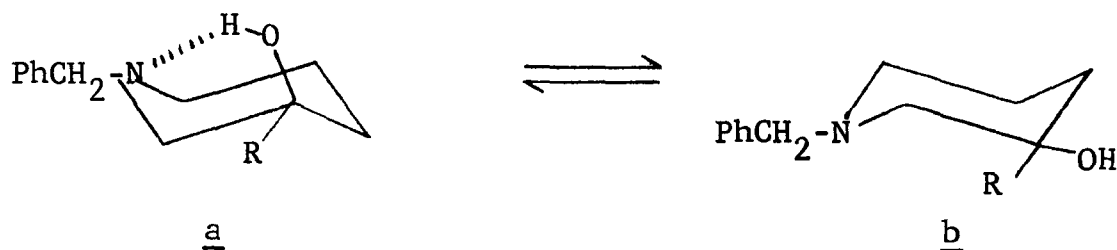
Using these calculations or the calibration curve, the composition of the conformational equilibria of a number of 3-piperidinols were estimated (see Table 8). From these data the conformation free energy differences ( $-\Delta G$ ) for a hydroxyl group capable of hydrogen bonding to nitrogen were determined. An analysis of the infrared spectrum of a 0.0025 molar solution of 1-methyl-3-piperidinol (3) in carbon tetrachloride has been shown to contain 57% of conformer 3b, which corresponds to a conformational free energy difference ( $-\Delta G$ ) of +0.18 kcal/mole at 37°. For comparison, a 26% solution of 3 in deuteriochloroform has a  $-\Delta G$  value of +0.33 kcal/mole at 40° as determined from an nmr analysis. On the other hand,



LeFevre<sup>24</sup> reported that the conformational free energy difference ( $-\Delta G$ ) for 1-methyl-4-piperidinol (27) under similar conditions was 0.82 kcal/mole. The difference between the data for 3 and that of 1-methyl-4-piperidinol (27) reflects the effect of the hydrogen bond. The conformational equilibria of 3 in non-basic solvents, like carbon tetrachloride, at high dilutions indicated that the conformer having an axial hydroxyl is more favored in 3 than in 27, since at these concentrations no intermolecular hydrogen bonding takes place. The agreement between the infrared and nmr data is quite remarkable considering the differences in concentration.

The effect of the variation of the substituent on the nitrogen atom on the conformational free energy difference ( $-\Delta G$ ) of 3-piperidinols was investigated by a study of the infrared bands due to hydroxyl stretching vibrations of unsubstituted (28), 1-methyl (3), 1-ethyl (29) and 1-benzyl (30)-3-piperidinols. It was found that as the size of the group attached to nitrogen increased from hydrogen to ethyl, the conformational free energy difference ( $-\Delta G$ ) decreased from +0.25 to 0.00 kcal/mole. Therefore, as the size of the group attached to nitrogen increased from hydrogen to ethyl, the mole percentage of the conformer having an axial hydroxyl that was bonded to nitrogen increased from 40% to 50%, which would be in the same order as the relative basicity. The exception to this was 1-benzyl-3-piperidinol (30) in which the conformational free energy difference ( $-\Delta G$ ) was +0.10 kcal/mole, and the mole percentage of conformer 30a was 46%. One possible rationalization of these data is that the basicity plays an important role in effecting the equilibria, but the steric bulk of the group attached to the nitrogen must also be considered.

The same analytical method appeared to be successful for the estimation of the conformational equilibria of tertiary alcohols such as 1-benzyl-3-methyl-3-piperidinol (42) and 1-benzyl-3-ethyl-3-piperidinol (43). An analysis of the infrared spectrum of a 0.00249 molar solution of 42 in carbon tetrachloride solution led to an estimate of the conformational equilibrium containing 83 mole percentage of conformer 42a. The analysis of a 0.00253 molar solution of 1-benzyl-3-ethyl-3-piperidinol (43) in carbon tetrachloride solution indicated that 86% of conformer 42a was present. Therefore, in comparison to a secondary alcohol such as 1-benzyl-3-piperidinol (30), disubstitution at the 3-position caused an increase in the conformer having the axial hydroxyl. It was shown by Bersch and Schon<sup>33</sup> that in 1-methyl-3-substituted-3-piperidinols the conformer having an axial hydroxyl group predominated. The larger the size of the group in the 3-position, the greater the excess of the conformer having the axial hydroxyl. The infrared spectrum of 1-benzyl-3-phenyl-3-piperidinol (38) showed only a single absorption band at  $3513\text{ cm}^{-1}$  due to intramolecular hydrogen bonding indicating that 38 existed entirely as the conformer having the axial hydroxyl. Therefore, as the size of the group at the 3-position increased from methyl to phenyl, the mole percentage of the conformer having the axial hydroxyl increased from 83% to 100%.

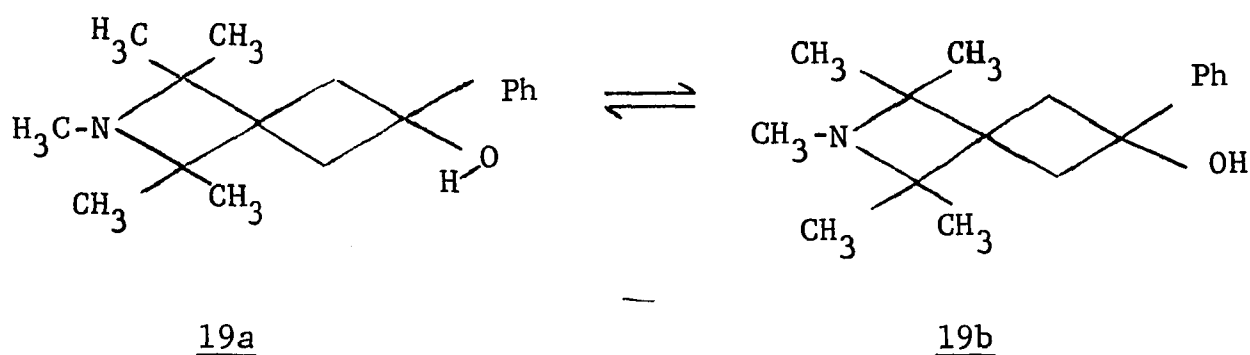


42, R = CH<sub>3</sub>

43, R = CH<sub>2</sub>-CH<sub>3</sub>

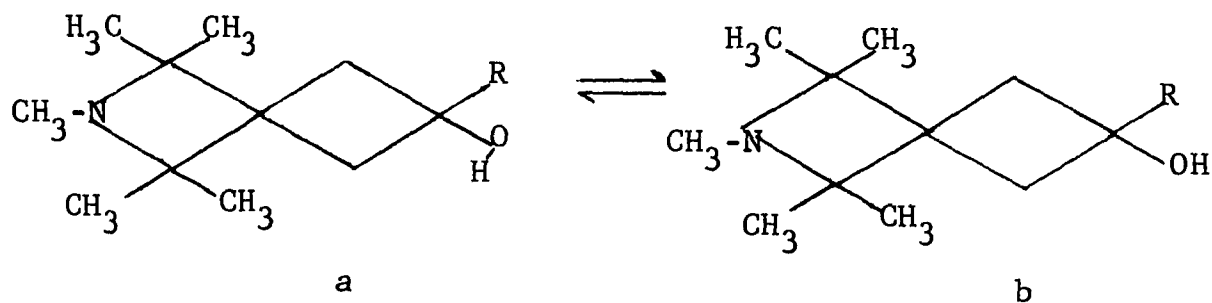
38, R = Ph

The composition of the conformational equilibria of various 4-piperidinols can also be estimated by this method. Lyle<sup>15</sup> reported that the conformational equilibrium of 1,2,2,6,6-pentamethyl-4-phenyl-4-piperidinol (19) contained chair and classical boat conformation: however, it is possible that the two hydroxyl bands arise from two non-chair conformations such as 19a and 19b. The concentration of the unbonded hydroxyl in the non-chair conformer 19b can be estimated from the plot of area of absorbance of unbonded hydroxyl vs the molar concentration.



To determine the effect of variation of the substituent at the 4-position on the conformational equilibria of the 1,2,2,6,6-pentamethyl-4-substituted-4-piperidinols, a study of 4-methyl-(44), 4-ethyl-(45), and 4-phenyl-(19) 1,2,2,6,6-pentamethyl-4-piperidinols was undertaken. A preliminary investigation of this effect was determined from the ratio of the area of the band for the unbonded hydroxyl plotted in transmittance ( $A_f$ ) to the area of the bonded hydroxyl band ( $A_b$ ). It was found that as the substituent in the 4-position increased in size from methyl to phenyl, the ratio  $A_f/A_b$  decreased from 0.63 to 0.33 (see Table 9). These data indicated that an increase in the size of the substituent in

the 4-position caused an increase in the proportion of the non-chair conformer having the hydroxyl bonded to nitrogen. Further evidence to support these data were the variations of the frequency shift between the bonded and unbonded hydroxyl absorption bands. It was found that in 1,2,2,4,6,6-hexamethyl-4-piperidinol (44) in which a methyl group is in the 4-position, the frequency shift between the bonded and unbonded hydroxyl absorption bands ( $\Delta \nu_{\text{OH}}$ ) was  $200 \text{ cm}^{-1}$ . On increasing the size of the substituent in the 4-position to a phenyl group, an increase in the  $\Delta \nu_{\text{OH}}$  shift to  $242 \text{ cm}^{-1}$  was observed (see Table 9). The larger the shift between the bonded and unbonded hydroxyl absorption bands, the stronger was the hydrogen bond to the nitrogen and the larger was the percentage of the non-chair conformers in which the hydroxyl was bonded to the nitrogen. These data support the relationship that as the size of the substituent in the 4-position is increased, the percentage of the non-chair conformer in which the hydroxyl is bonded to nitrogen is increased.

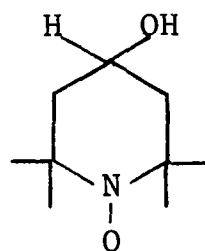
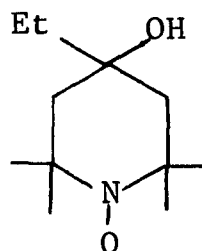
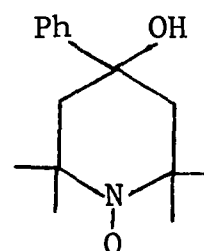


R = CH<sub>3</sub>, 44

R = Et, 45

A quantitative estimation of the composition of the conformational equilibria of 1,2,2,4,6,6-hexamethyl-4-piperidinol (44) and 1,2,2,6,6-pentamethyl-4-ethyl-4-piperidinol (45) was determined from the plot of the area of the absorbance band of the unbonded hydroxyls vs the molar concentration. A 0.00208 molar solution of 1,2,2,4,6,6-hexamethyl-4-piperidinol (44) in carbon tetrachloride solution contained 58% of the non-chair conformer 44b in which the hydroxyl was unbonded, and a 0.00116 molar solution of 45 in carbon tetrachloride solution contained 54% of the non-chair conformer 45b. It was noted that 1,2,2,4,6,6-hexamethyl-4-piperidinol (44) had a larger percentage of the non-chair conformer in which the hydroxyl was unbonded than did its 4-ethyl analog (45). These data are in agreement with the preliminary results found with the spectra plotted in transmittance.

It has been reported that stable free radicals of the 2,2,6,6-tetramethyl piperidine nitrogen oxide series have been synthesized.<sup>34,35,36</sup> Evidence to support the existence of these compounds as free radicals was the electron spin resonance (esr) data that were obtained. In the solid state the 2,2,6,6-tetramethyl piperidine nitrogen oxide radicals displayed an esr singlet, while in benzene solution the esr singlet exhibited by the radicals became a triplet.

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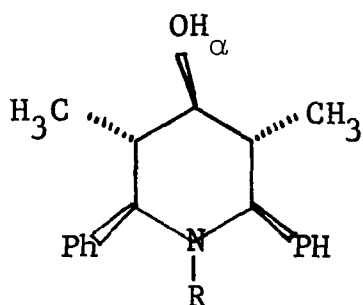
To determine whether hydrogen bonding would take place between a hydroxyl group and a radical oxygen in compounds of this type, a study of 2,2,6,6-tetramethyl-4-phenyl-4-piperidinol nitrogen oxide (48) was undertaken. It had been reported by Rassat and coworkers<sup>34</sup> that the infrared spectrum of a 0.01 molar solution of 2,2,6,6-tetramethyl-4-piperidinol nitrogen oxide (46) in carbon tetrachloride solution showed a single unbonded hydroxyl absorption at  $3620\text{ cm}^{-1}$ . These authors concluded that there was no intramolecular hydrogen bonding taking place in 46. Rozantzev and Neiman<sup>35</sup>, however, reported that the infrared spectrum of 2,2,6,6-tetramethyl-4-ethyl-4-piperidinol nitrogen oxide (47) displayed narrow and broad bands in the  $3605\text{ cm}^{-1}$  and  $3445\text{ cm}^{-1}$  regions, respectively. Although the concentration of this solution was not reported, these data suggested that hydrogen bonding of the hydroxyl with nitrogen was occurring. The lack of sufficient data led us to investigate the infrared spectrum of 2,2,6,6-tetramethyl-4-phenyl-4-piperidinol nitrogen-oxide (48). The infrared spectrum of a 0.005 molar solution of 48 in carbon tetrachloride solution showed a single  $\pi$ -bonded hydroxyl absorption band at  $3606\text{ cm}^{-1}$ . This evidence indicated that hydrogen bonding of the hydroxyl did not occur with the radical oxygen and also no bonding to nitrogen was present. It had been reported by Rozantzev<sup>36</sup> that with 2,2,6,6-tetramethyl-4-piperidinol nitrogen oxide (46), 73% of the free radical was located at oxygen and 27% at nitrogen. In light of these findings, it is possible that for hydrogen bonding to occur the oxygen cannot have an unpaired electron.

In conclusion, the nmr analysis of the coupling constants to determine the conformational equilibria is limited to secondary piperidinols without substitution at the  $\beta$  position; however, the infrared analysis of the conformational

equilibria can be extended quantitatively not only to 3- and 4-piperidinols, but also to an infinite variety of other systems. The infrared spectroscopic technique also allows the study of very dilute solutions.

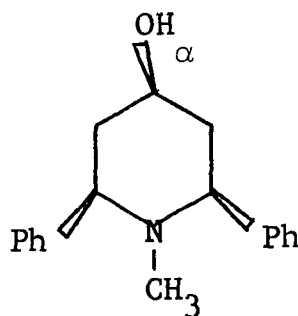
CONFORMATIONAL STUDY OF  
3,5-DIMETHYL-2,6-DIPHENYL-4-PIPERIDINOLS

Non-chair conformations have been reported by Balasubramanian and Padma<sup>37</sup> for the  $\alpha$ -isomer of 1,3,5-trimethyl-2,6-diphenyl-4-piperidinol (49a). The infrared spectrum of 49a was reported by Chen and LeFevre<sup>38</sup> to show two distinct peaks at  $3626\text{ cm}^{-1}$  and  $3588\text{ cm}^{-1}$ , which were assigned as the un-bonded and intramolecularly hydrogen bonded hydroxyl, respectively. Chen and LeFevre proposed (for the conformer of 49a) a classical boat in which intramolecular hydrogen bonding occurred between the hydroxyl at the 4-position and the heterocyclic nitrogen. These authors also reported that the contribution from a boat conformation is greater in 49a than in  $\alpha$ -1-methyl-2,6-diphenyl-4-piperidinol (39), which does not show any intramolecular hydrogen bonding. The presence of such a boat conformation, however, has been questioned both on the basis of the weak bond indicated by the small difference in frequency between the two OH absorption bands<sup>20</sup>, and on conformational grounds.<sup>39</sup>

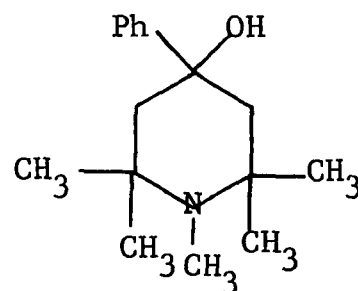


49a R = CH<sub>3</sub>

40a R = H



39



19



Tichy<sup>20</sup> questioned this postulate on the basis of the small frequency shift observed, for the  $\Delta\nu_{\text{OH}}$  value ( $39\text{ cm}^{-1}$ ) found in the spectrum of the "hexa-equatorial" isomer of  $\alpha$ -1,3,5-trimethyl-2,6-diphenyl-4-piperidinol (49a) did not appear to be sufficiently large to be due to an OH $\cdots$ N bond. Tichy had based his reasoning on the results reported by Lyle<sup>15</sup> for 1,2,2,6,6-pentamethyl-4-phenyl-4-piperidinol (19), where a large  $\Delta\nu_{\text{OH}}$  value ( $205\text{ cm}^{-1}$ ) had been demonstrated for a boat conformation. Aaron and Rader<sup>19</sup> suggested that 1,3,5-trimethyl-2,6-diphenyl-4-piperidinol (49a) existed in a twist conformation rather than a classical boat conformation. The weak intramolecular hydrogen bond should be assigned as either a weak OH $\cdots$ N or an OH $\cdots$  phenyl interaction.

The significant participation of a boat conformation in the conformational equilibrium of  $\alpha$ -1,3,5-trimethyl-2,6-diphenyl-4-piperidinol (49a) was questioned on the basis of comparison of non-bonded interactions.<sup>39</sup> Although the hydrogen bond tends to stabilize the boat form and the gauche interactions of the hydroxyl with the methyls tend to destabilize the chair, these energies would not be expected to equal or exceed the 1,3-non-bonded interaction between the axial 3- and 5-methyls in the boat form and the other unfavorable interaction of the boat form.

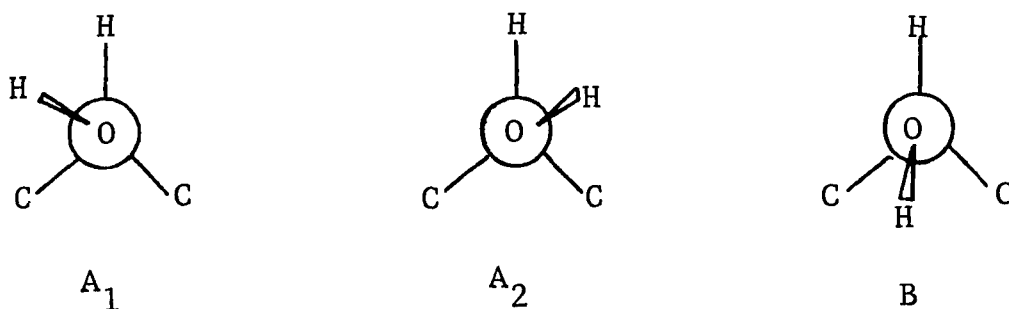
The lack of any obvious reason why  $\alpha$ -1,3,5-trimethyl-2,6-diphenyl-4-piperidinol (49a) should exist as a conformational equilibrium between a chair and boat form led to a re-examination of the experimental data reported by Chen and LeFevre.<sup>38</sup> Experimentally, the separation of the isomers of the 3,5-dimethyl-2,6-diphenyl-4-piperidinols was achieved by column chromatography. The reduction products obtained from the reaction of lithium aluminum hydride with 1,3,5-trimethyl-2,6-diphenyl-4-piperidone were separated on a Florisil column to give two isomers. The  $\beta$  isomer of 1,3,5-trimethyl-2,6-

diphenyl-4-piperidinol (49b) was eluted in the petroleum ether-benzene (1:1) fractions. The nmr spectrum indicated that it was of greater than 91% of the axial isomer (49b). The  $\alpha$ (equatorial) isomer (49a) was eluted in the benzene-ether (1:1) fractions with less than 10% contamination by the  $\beta$  isomer, indicated by analysis of the 3,5-dimethyl protons in the nmr. The  $\alpha$  and  $\beta$  isomers of 3,5-dimethyl-2,6-diphenyl-4-piperidinol (40) were separated by column chromatography using a neutral alumina column. The benzene fractions gave 100% of the  $\beta$  isomer (40b), while the  $\alpha$  isomer (40a) was eluted in the ether fractions in greater than 89% purity as determined by nmr analysis of the 3,5-dimethyl protons. The failure to isolate all of the isomers in a pure state may have resulted from equilibration of the two isomers on the column.

The infrared spectra of the two isomers of 1,3,5-trimethyl-2,6-diphenyl-4-piperidinol (49a) and 3,5-dimethyl-2,6-diphenyl-4-piperidinol (40a) were examined in carbon tetrachloride solutions of 0.005 molar concentration. Two absorption bands which could be assigned to hydroxyl stretching vibrations were evident (see Table 4). The comparison of these two absorption bands with the unbonded hydroxyl ( $3612\text{ cm}^{-1}$ ) of trans-1-methyl-4-phenyl-3-piperidinol (32) showed that the lower frequency of an unbonded or weak  $\pi$ -bonded hydroxyl and indeed the second band at higher frequency ( $3652\text{ cm}^{-1}$ ) was the unusual absorption band (see Figure X). These data suggested that Lefevre's interpretation<sup>38</sup> that hydrogen bonding caused the lower frequency absorption was incorrect. Rather the two distinct bands were caused by some structural feature which increased the frequency of the hydroxyl stretching vibration. Similar results have been noted with a number of hindered alcohols (see Table 4).

It has been shown that the rotational conformers of

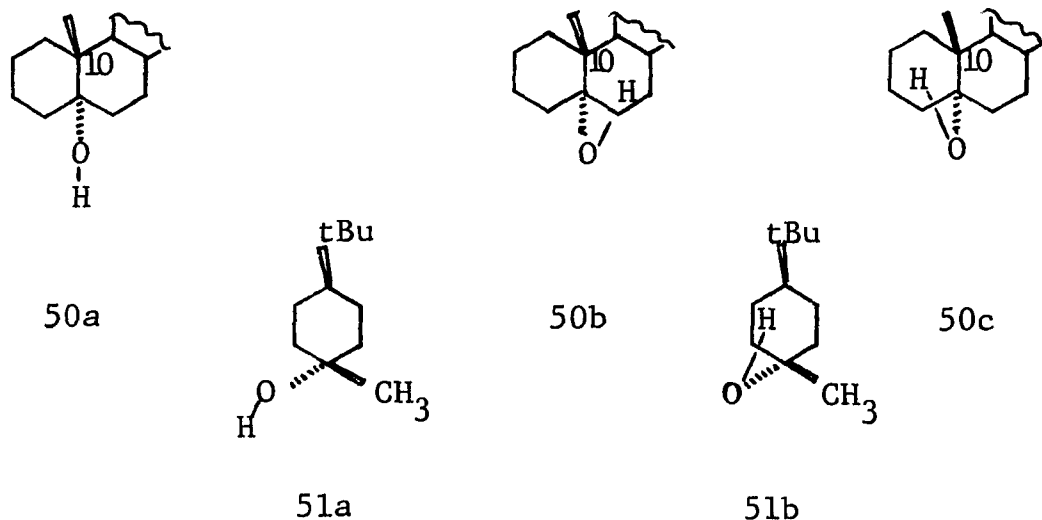
alcohols lead to absorption bands with different energies and, therefore, different frequencies.<sup>11,40</sup> Aaron and Rader<sup>11</sup> reported that in a six-membered ring the equatorial alcohols, with three rotational conformations, show an unsymmetrical OH absorption band while the axial alcohol, capable of only two rotational conformers that are energetically favorable, gives a symmetrical absorption. Meakins and coworkers<sup>41</sup> found in certain cases for an equatorial hydroxyl that this unsymmetrical band could be resolved into two distinct bands which could be assigned to the presence of rotational conformers having different orientations of the O-H bond. This explanation recognizes the existence of rotational conformations of the hydroxyl group, designated in secondary alcohols as rotamer type A and B, which differ slightly in the position of their absorption maxima, A being greater than B by about  $10\text{ cm}^{-1}$ . Thus, the observed free OH band represents a composite of the bands of individual rotamers, each contributing according to its relative population.



If one applies this correlation to a piperidinol system, one concludes that both rotamer types A and B should be present, when the hydroxyl group is equatorial.<sup>19</sup> In an axial hydroxyl system, however, the population of rotamer B

should be severely restricted due to steric interactions of the axial 2,6-hydrogens of the piperidinol with the hydroxyl hydrogen as shown in Figure XI, conformer 6. For piperidinols, the two rotamers  $A_1$  and  $A_2$  should be essentially equivalent in the immediate steric environment.

Meakins et. al.<sup>41</sup> reported that in the infrared spectrum of 5 $\alpha$ -cholestan-5 $\alpha$ -ol (50), which has a tertiary axial hydroxyl, the higher frequency band ( $3629\text{ cm}^{-1}$ ) can be assigned to the exo-form 50a and the second band ( $3619\text{ cm}^{-1}$ ) to two equivalent endo forms (50b and 50c). The infrared spectrum of trans-1-methyl-4-*t*-butyl-cyclohexanol (51), however, showed only a single band at  $3616\text{ cm}^{-1}$ . In contrast to 5 $\alpha$ -cholestan-5 $\alpha$ -ol (50), trans-1-methyl-4-*t*-butyl-cyclohexanol (51) had two equivalent exo forms, such as 51a, and one endo form 51b. The absence of the second hydroxyl band in the infrared spectrum of 51 was attributed to a higher proportion of molecules adopting the exo form 51a. Meakins et. al.<sup>41</sup> reported that the frequency difference between the bands of the exo forms (50a and 51a) arose from the presence of a staggered quarternary carbon ( $C_{10}$ ) in 50a, which caused the increase in frequency. In the exo form (50a) the  $C_{10}$  carbon was trans and coplanar with the O-H bond.



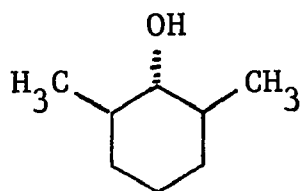
The assignment of the rotational isomers of the 3,5-dimethyl-2,6-diphenyl-4-piperidinols (40 and 49) have been noted. In the infrared spectrum of  $\alpha$ -1,3,5-trimethyl-2,6-diphenyl-4-piperidinol (49a), which has a secondary equatorial hydroxyl, the high frequency absorption ( $3652\text{ cm}^{-1}$ ) can be assigned to the two equivalent rotational conformers (Figure XI, conformers 1 and 2) having the hydroxyl O-H trans and coplanar with the substituted carbons at the 3 and 5 positions. The second band at  $3615\text{ cm}^{-1}$  can be assigned to the one rotational conformer (Figure XI, conformer 3) having the hydroxyl O-H trans and coplanar to the carbinol proton. In contrast to  $\alpha$ -1,3,5-trimethyl-2,6-diphenyl-4-piperidinol (49a), the infrared spectrum of the  $\beta$  isomer (49b), which contained an axial hydroxyl, showed a single hydroxyl absorption at  $3650\text{ cm}^{-1}$ . This high frequency absorption ( $3650\text{ cm}^{-1}$ ) can be assigned to the two rotational conformers (Figure XI, conformers 4 and 5) having the hydroxyl hydrogen trans and coplanar with the substituted carbons at the 3 and 5 positions. The absence of the second band in the infrared spectrum of 49b was attributed to the fact that the population of the rotational conformer (Figure XI, conformer 6) having the hydroxyl hydrogen trans and coplanar to the carbinol proton, was unfavorable due to the unfavorable non-bonded interactions of the axial 2,6-protons with the hydroxyl hydrogen.

It is quite evident with these compounds that three rotational conformers are possible and that the relative populations of the conformations from a steric consideration lead to a rough approximation of the relative intensity of the two bands.<sup>11</sup> The high frequency absorption always resulted from the two rotational conformers which had a highly substituted  $\beta$  carbon trans and coplanar to the O-H bond, while the low frequency absorption resulted from the rotational conformer

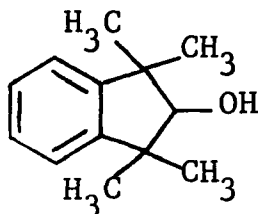
with the carbinol protons trans and coplanar to the O-H bond (Figure XI, conformer 3). If the rotational conformers have equal populations, then the area of the high frequency absorption should be about twice the area of the lower frequency absorption in the equatorial isomer. This proved to be correct from the infrared spectrum of a 0.00195 molar solution of  $\alpha$ ,3,5-dimethyl-2,6-diphenyl-4-piperidinol (40a) in carbon tetrachloride solution, which showed two distinct hydroxyl stretching vibrations at  $3652\text{ cm}^{-1}$  and  $3614\text{ cm}^{-1}$ , whose respective areas of absorbance were 6.19 sq. in. and 3.11 sq. in., the area of the  $3652\text{ cm}^{-1}$  peak being 1.99 times as large as that of the  $3614\text{ cm}^{-1}$  peak (see Figure V, curve H).

If these interpretations are correct, no intramolecular hydrogen bonding is needed to explain the presence of the two distinct bands in the infrared spectra of the 3,5-dimethyl-2,6-diphenyl-4-piperidinols (40a and 49a), and as a result, the earlier conformational assignments by Chen and LeFevre<sup>38</sup> based on these data would not be correct.

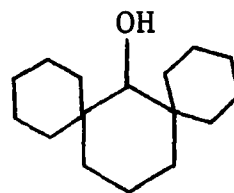
Evidence to support these conclusions about the 3,5-dimethyl-2,6-diphenyl-4-piperidinols (40 and 49) was obtained from a study of a number of other hindered alcohols (see Table 4). trans-2-trans-6-Dimethylcyclohexanol (52a) was separated by preparative gas chromatography from the three isomers obtained from the lithium aluminum hydride reduction of 2,6-dimethylcyclohexanone.<sup>42</sup> The infrared spectrum of trans-2-trans-6-dimethylcyclohexanol (52a) clearly indicated that a heterocyclic nitrogen and the 2,6-diphenyl groups were not necessary to have two absorption bands in the  $3650\text{--}3600\text{ cm}^{-1}$  region of the spectrum. trans-2-trans-6-Dimethylcyclohexanol (52a) gave two hydroxyl stretching vibrations, one at  $3652\text{ cm}^{-1}$  and another at  $3614\text{ cm}^{-1}$  due to rotational conformers of the O-H bond (see Table 4).



52a

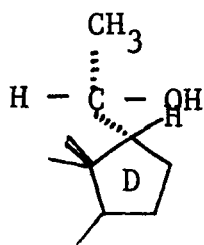


53

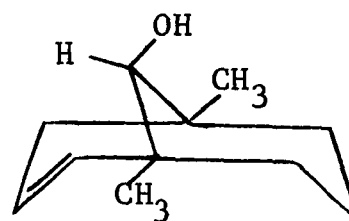


54

Similar results were also noted in other non-heterocyclic, sterically-hindered alcohols, 1,1,3,3-tetramethylindan-2-ol (53) and dispiro-2,6-cyclohexyl cyclohexanol (54) (see Table 4). Other monohydric secondary alcohols have been reported to give comparable results. Meakins et. al.<sup>41</sup> reported that in the infrared spectra of 5- $\alpha$ -cholestan-7- $\beta$ -ol (55) and 2,2,4,4-tetramethyl-3-pentanol (56), the hydroxyl stretching vibration appeared as two distinct bands which resulted from the presence of rotational conformers having different orientations of the O-H bond. Similarly Danilewicz et. al.<sup>43</sup> found that 5- $\alpha$ -17 $\alpha$ -pregnan-20- $\alpha$ -ol (57) and the corresponding 20- $\beta$ -ol each gave two bands in the 3650-3600  $\text{cm}^{-1}$  region of the spectrum (see Table 4). Eglington and coworkers<sup>44</sup> found analogous results in the bicyclo [3,3,1] nonane system. It was reported that the anti isomer of 1,5-dimethylbicyclo [3,3,1] non-2-en-9-ol (58) gave a hydroxyl absorption band at 3640  $\text{cm}^{-1}$  and a shoulder at 3625  $\text{cm}^{-1}$ . Similarly, the infrared spectrum of 1,5-dimethylbicyclo[3,3,1]nonan-9-ol (59), showed hydroxyl absorption bands at 3643  $\text{cm}^{-1}$  and 3625  $\text{cm}^{-1}$  (see Table 4).



57

anti 58

The infrared spectra of 1,3,5-trimethyl-2,6-diphenyl-4-piperidinol (49a) and trans-2-trans-6-dimethylcyclohexanol (52) were carried out in various solvents at 0.005 molar concentration, to determine the effect that these solvents had on the hydroxyl stretching vibration (see Table 10). In each of these compounds, the two distinct bands were present in the various solvents; however, these bands shifted to different frequencies depending on the solvent used. In an n-hexane solution of 49a, the frequency of absorption was the highest ( $3655\text{ cm}^{-1}$  and  $3615\text{ cm}^{-1}$ ), due to little or no bonding of the solvent to the hydroxyl hydrogen. In carbon disulfide the frequency of both hydroxyl absorptions of 49a and 52 were shifted down by  $20\text{ cm}^{-1}$ , indicating a stronger bonding of the hydroxyl with solvent. It was found that in carbon tetrachloride solutions of 49a and 52, the frequency of absorption was close to that observed in n-hexane. The infrared spectrum of 1,2,2,6,6-pentamethyl-4-piperidinol (37), however, showed a hydroxyl stretching vibration at  $3630\text{ cm}^{-1}$ , which was at approximately  $20\text{ cm}^{-1}$  lower frequency in carbon tetrachloride than for 49a and 52 (see Table 10). These data suggested that the methyl groups in the  $\beta$  position of 49a and 52 interfered sterically with bonding of the solvent with the hydroxyl. The effect of the solvent on the frequency of the high frequency



absorption could not be explained on this basis, however.

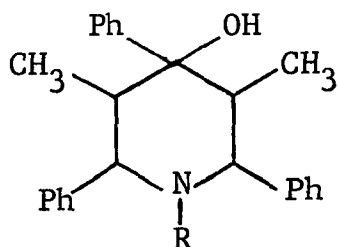
Examination of the models of 3,5-dimethyl-2,6-diphenyl-4-piperidinols (40 and 49) shows that in the equatorial isomers, the two rotational conformers having the hydroxyl O-H bond trans and coplanar with the substituted carbons at the 3 and 5 positions has the hydroxyl proton near a methyl group as shown in Figure XI, conformers 1 and 2. The axial isomer having only the two rotational conformers in which the hydroxyl O-H bond is trans and coplanar to the substituted carbons has the hydroxyl proton similarly oriented such that it is hindered by the near methyl group (see Figure XI).

It is evident that the absorption of high frequency resulted from the rotational conformers with a highly substituted  $\beta$  carbon trans and coplanar to the O-H bond. These data suggest that the high frequency hydroxyl absorption is due to the highly substituted carbon near the hydroxyl group. Inductive effects should cause a decrease in frequency so the effect must be steric.

1,3,5-Trimethyl-2,4,6-triphenyl-4-piperidinol (60) and 3,5-dimethyl-2,4,6-triphenyl-4-piperidinol (61) were prepared by the addition of phenyl lithium to the corresponding ketones. The infrared spectra of 60 and 61 showed only a single hydroxyl stretching vibration at  $3621\text{ cm}^{-1}$  and  $3624\text{ cm}^{-1}$ , respectively. These frequencies are lowered a little due to a weak O-H bond with the geminal phenyl substituent. Therefore, the phenyl group in the 4-position of 60 and 61 did not destabilize the chair form and favor a non-chair conformation, for no intramolecular hydrogen bonding to nitrogen was observed. The hydroxyl stretching vibrations were at high frequencies for tertiary alcohols, although similar hydroxyl absorption in the infrared spectra have been noted for other tertiary alcohols,

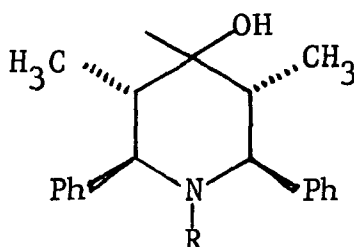
such as 5 $\alpha$ -cholestan-5 $\beta$ -ol<sup>41,44</sup> and tetrahydromarrubiin.<sup>45</sup>

It is clear, therefore, that the presence of two absorption bands in the OH stretching region does not require the postulation of non-chair conformations for the  $\alpha$  isomers of the 3,5-dimethyl-2,6-diphenyl-4-piperidinols (40a and 49a). The remaining evidence of non-chair conformations was based on the nmr spectra of these compounds and specifically on the observed coupling constants between the 4-proton and the adjacent hydrogens. Chen and LeFevre<sup>38</sup> found that the  $J_{aa}$  for the carbinol proton decreases from 11 cps in 39 to 9.7 cps in 49a. LeFevre indicated that this decrease in coupling constant was consistent with the fact that 49a existed in part in boat forms. These authors assumed that 39 exists almost exclusively in a chair conformation, then by taking the  $J_{aa} = 11.0$  cps and  $J_{ee} = J_{ae} = 2.5$  cps (from  $J_{ae}$  of 49b), calculated the maximum contribution of the classical boat conformation for 49a to be 16%.



60 R = CH<sub>3</sub>

61 R = H



49a R = CH<sub>3</sub>

40a R = H

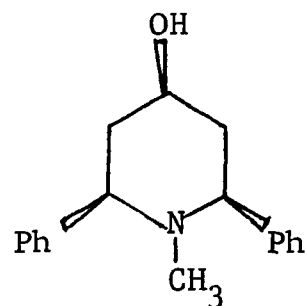
49b R = CH<sub>3</sub>

Isomer

$\alpha$

$\alpha$

$\beta$

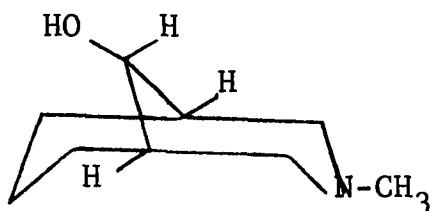


39

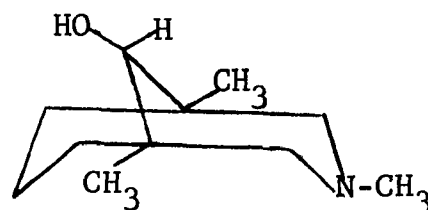
It has been shown that the coupling constants obtained from models having no vicinal substituents cannot be used for analysis of conformational equilibria of compounds which do have vicinal substituents.<sup>26</sup> This research determined that the limiting values of the coupling constants used for the conformational analysis of 1-methyl-4-piperidinol (27) was not appropriate for the conformational analysis of trans-1-methyl-4-phenyl-3-piperidinol (32) having a phenyl group on the carbon adjacent to the hydroxyl.<sup>26</sup> Therefore, Chen and LeFevre<sup>38</sup> made an incorrect estimation of the composition of the conformational equilibrium of  $\alpha$ -1,3,5-trimethyl-2,6-diphenyl-4-piperidinol (49a), which contains methyl groups in the  $\beta$  position, since the authors used the limiting coupling constants obtained from 2,6-diphenyl-4-piperidinol (39), which contained no  $\beta$  substituents. There is no evidence, therefore, that a non-chair conformer exists for the 3,5-dimethyl-2,6-diphenyl-4-piperidinols (40a and 49a).

Meakins and coworkers<sup>41</sup> reported that a shift of the infrared absorption band due to the hydroxyl stretching vibration of hindered alcohols to higher frequency was due to  $\beta$  substitution, regardless of conformation. In order to determine the effect of the conformation at the  $\beta$  position on the hydroxyl stretching vibration in hindered alcohols, 3-methyl-3-azabicyclo[3,3,1] nonan-9-ol (62) and 1,3,5-trimethyl-3-azabicyclo[3,3,1] nonan-9-ol (63) were studied.<sup>46</sup> In 3-methyl-3-azabicyclo[3,3,1] nonan-9-ol (62) two methylene groups are axial in the  $\beta$  position and do not provide steric interference to the stretching vibration of the hydroxyl group. In 1,3,5-trimethyl-3-azabicyclo[3,3,1] nonan-9-ol (63), two equatorial methyls are close enough to interfere with the vibration of the hydroxyl group. The infrared spectrum of 62 in carbon tetrachloride solution showed an unbonded hydroxyl stretching

vibration at  $3631\text{ cm}^{-1}$ , while the infrared spectrum of 63 in carbon tetrachloride solution showed a higher frequency absorption at  $3647\text{ cm}^{-1}$  with a shoulder at  $3631\text{ cm}^{-1}$  (see Table 4). The absorption at  $3647\text{ cm}^{-1}$  in 63 suggested that the equatorial methyls in the  $\beta$  position to the hydroxyl provide a steric interference to the stretching vibration, increasing the energy required for this absorption. Obviously, substitution alone in the  $\beta$  positions is not sufficient to cause a shift of the stretching absorption to the higher frequency.



62



63

Table 4

## Hydroxyl Stretching Frequencies of 3-Piperidinols

 $5 \times 10^{-3} \text{M CCl}_4$ 

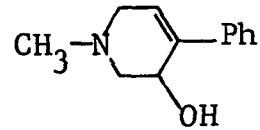
Substituted 3-Piperidinol	OH unbonded $\text{cm}^{-1}$	OH bonded $\text{cm}^{-1}$	$\Delta V$ $\text{cm}^{-1}$	Source
Unsubstituted (28)	3631	3532	99	42
1-Methyl (3)	3625	3535	90	42
1-Ethyl (29)	3631	3532	99	42
1-Benzyl (30)	3630	3545	85	61
1-Methyl-4-phenyl				
<u>cis</u> (31)	3607 <sup>b</sup>	3527	80	26,63
<u>trans</u> (32)	3612*			26,62
<hr/>				
1-Benzyl-3-Methyl (42)	3625	3527	98	61
1-Benzyl-3-Ethyl (43)	3628	3531	97	61
1-Benzyl-3-Phenyl (38)	--	3513	C=O <sup>---</sup> H (3454) 87	61
1-Benzoyl (65)	3628	3541		
1-Methyl-4,4-Diphenyl (64)	3605*	3483	122	63
	3610*	3562	48	63
1-Methyl-3,4-Diphenyl	--	3473	--	63

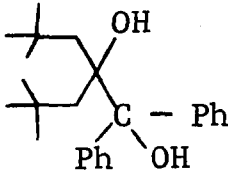
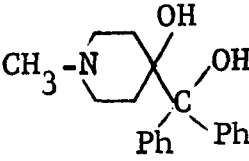
Table 4

Hydroxyl Stretching Frequencies of 4-Piperidinols  
 $5 \times 10^{-3} \text{ M } \text{CCl}_4$

2,2,6,6-Tetramethyl 4-Piperidinol	OH unbonded $\text{cm}^{-1}$	OH bonded $\text{cm}^{-1}$	$\Delta V$ $\text{cm}^{-1}$	Source
1-Methyl (37)	3630			61
1-Methyl-4-Phenyl (19)	3612 <sup>a</sup>	3370	242	61
1-Methyl-4-Ethyl (45)	3616	3400	216	61
1,4-Dimethyl (44)	3619	3419	200	61
4-Phenyl (66)	3610 <sup>a</sup>	3393	217	61
4 Phenyl N-oxide (48)	3606 <sup>a</sup>	--	--	61
<hr/>				
4-Piperidinols				
1-Methyl (27)	3632	--		42
1-Methyl-4-Phenyl (20)	3615 <sup>a</sup>	--		63
1-Benzyl	3630	--		42
1-Methyl-2,6-Diphenyl (39) ( $\alpha$ )	3628	--		61
1-Methyl-2,6-Diphenyl				
1-Methyl 4-Methyl (41)	3621	--		61
1-Methyl 4-Phenyl	3612	C=O .....HO		64
1-Methyl - 4-Benzoyl	3610 <sup>a</sup>	3476	134	65
1-Methyl - 4-Cyano	C $\equiv$ N .....HO 3590			
1-Methyl - 4-Benzyl	3612 <sup>a</sup> (sh)	$\pi$ .....HO 3595	17	66

Table 4

## Hydroxyl Stretching Frequencies of Piperidinols

Tropanols	OH unbonded cm <sup>-1</sup>	OH bonded cm <sup>-1</sup>	$\Delta V$ cm <sup>-1</sup>	Source
1-Methyl-3-Phenyl 3-Tropanol	3612 <sup>a</sup>	--	--	64
1-Methyl-3-Phenyl- 2 $\alpha$ Tropanol	3615 <sup>a</sup>	--	--	64
-Tropane	3630	--	--	
L-2 $\beta$ Tropanol ( <u>5a</u> )	--	3478	--	67
<hr/>				
Piperidin-diols				
1-Methyl-4-Phenyl- piperidin-3,4 diol	3619 <sup>a</sup>	3508	111	63
1,2,2,6,6-Pentamethyl- 4-phenyl-piperidin- 3,4-diol	3610 <sup>a</sup>	3567	43	63
	3623	3581	3423 3290	48
	3605	3581	24	68

---

continued -

Table 4 cont'd

<u>Compound</u>	<u>Infrared Bands</u> <u>cm<sup>-1</sup></u>		<u>Absorption</u>	<u>Ref.</u>
2,2,4,4-Tetramethyl-3-pentanol ( <u>56</u> )	3651	3626		41
5 $\alpha$ ,17 $\alpha$ -Pregnan-20 $\alpha$ -ol ( <u>57</u> )	3648	3622		43

## Hydroxyl Stretching Vibrations of Hindered Alcohols

<u>Compound</u>		<u>Infrared Bands</u>		<u>Source</u>
<u>3-azabicyclo[3.3.1]nonan-9-ols</u>				
3-Methyl	( <u>62</u> )		3631	46
1,3,5-Trimethyl	( <u>63</u> )	3647	3631(sh)	46
3,9-Dimethyl		3637(sh)	3621 cm <sup>-1</sup>	46
1,3,5,9-Tetramethyl		3636 cm <sup>-1</sup>		46
<u>bicyclo[3.3.1]nonan-9-ols</u>				
1,5-Dimethyl	( <u>59</u> )	3643	3625(sh)	44
<u>anti</u> 1,5-Dimethyl(2-en)	( <u>58</u> )	3640	3625(sh)	44



Table 4 cont.

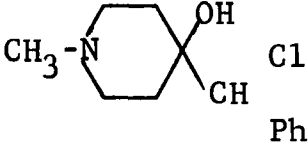
	OH unbonded cm <sup>-1</sup>	OH bonded cm <sup>-1</sup>	$\Delta V$ cm <sup>-1</sup>	Source
<u>trans</u> -2-Phenylcyclo- hexanol (34)	3628	HO 3607		61
1-Phenylcyclohexanol	3615			42
1-Methyl-4-phenyl-3- bromo-4-piperidinol	3612 <sup>a</sup>	Br HO 3579(Sh)	33	63
	3626	3579	47	
1-Quinolizidinols				
<u>trans</u> 1,10-H	3642			69
<u>cis</u> 1,10-H		3545		69

Table 4

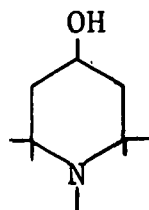
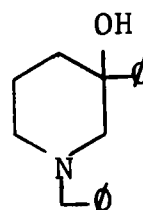
## Hydroxyl Stretching Vibrations of Hindered Alcohols

<u>Compound</u>	<u>Infrared Bands cm<sup>-1</sup></u>		<u>Other Absorption</u>	<u>Ref.</u>
$\alpha$ -1,3,5-Trimethyl-2,6-diphenyl-4-piperidinol ( <u>49a</u> )	3652	3615		61
$\beta$ -1,3,5-Trimethyl-2,6-diphenyl-4-piperidinol ( <u>49b</u> )	3650	----		61
$\alpha$ -3,5-Dimethyl-2,6-diphenyl-4-piperidinol ( <u>40a</u> )	3652	3614	3334 (NH)	61
$\beta$ -3,5-Dimethyl-2,6-diphenyl-4-piperidinol ( <u>40b</u> )	3654	----	3332 (NH)	61
1,3,5-Trimethyl-2,4,6-triphenyl-4-piperidinol ( <u>60</u> )	3621	----		61
3,5-Dimethyl-2,4,6-triphenyl-4-piperidinol ( <u>61</u> )	3624	----	3332 (NH)	61
<u>trans</u> -2- <u>trans</u> -6-Dimethyl-cyclohexanol ( <u>52a</u> )	3652	3614		61
1,1,3,3-Tetramethyl-2-indanol ( <u>53</u> )	3642	3628		70
2,6-Dimethylcyclohexan-1,4-diol	3643		3624 (4-OH)	71
5 $\alpha$ -Cholestan-7 $\beta$ -ol ( <u>55</u> )	3650	3619		41

continued -

Table 5

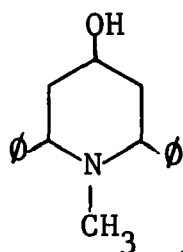
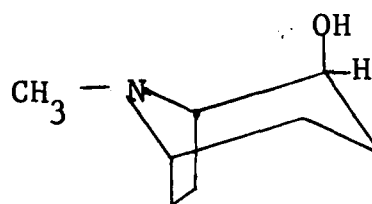
Integrated Intensities of Hydroxyl Absorption Bands  
Mixtures of Model Compounds

3738

<u>Bonded</u>	$\frac{[F]}{[b]}$	Wt. of 37 (mg.)	Wt. of 38 (mg.)	Conc. $\times 10^{+3} M$	$\frac{AF}{Ab}$
28.0	2.57	7.935	4.811	2.58	$\frac{634}{736} = .865$
37.5	1.69	6.698	6.206	2.50	$\frac{587}{942} = .623$
50.4	0.99	5.413	8.604	2.56	$\frac{503}{1345} = .374$
62.5	0.60	4.002	10.488	2.51	$\frac{375}{1700} = .22$
73.3	0.365	2.800	12.086	2.47	$\frac{302}{1820} = .166$
85.8	0.165	1.498	14.228	2.48	$\frac{212}{2178} = .098$

continued -

Table 5 cont'd

395a

<u>Bonded</u>	<u><math>\frac{[F]}{[b]}</math></u>	<u>Wt. of 37 (mg.)</u>	<u>Wt. of 38 (mg.)</u>	<u>Conc. <math>\times 10^3 M</math></u>	<u><math>\frac{AF}{Ab}</math></u>
38.4	1.64	10.552	3.395	2.53	$\frac{665}{825} = .806$
49.0	1.08	8.432	4.084	2.42	$\frac{457}{952} = .48$
58.5	0.71	6.576	4.948	2.39	$\frac{401}{1262} = .32$
73.3	0.365	4.447	6.490	2.51	$\frac{348}{1537} = .22$
82.7	0.21	3.550	8.781	2.52	$\frac{316}{1775} = .178$

Table 6

## Integrated Intensities of Bonded Hydroxyl Groups

## 1) 1-Benzyl-3-phenyl-3-piperidinol (38)

<u>molar conc.</u>	<u>mg/25 ml</u>	<u>Abs. area</u>	<u>E<sub>A</sub> x 10<sup>3</sup></u>
.00073	4.811	.736	10.1
.00093	6.206	.942	10.1
.00129	8.604	1.345	10.4
.00157	10.488	1.700	10.8
.00181	12.086	1.820	10.0
.00213	14.228	2.178	10.2

2) L-2 $\beta$ -tropanol (5a)

<u>molar conc.</u>	<u>mg/25 ml</u>	<u>Abs. area</u>	<u>E<sub>A</sub> x 10<sup>3</sup></u>
.00096	3.395	.825	8.6
.00116	4.084	.952	8.2
.00140	4.948	1.262	9.0
.00184	6.490	1.537	8.4
.00208	8.781	1.775	8.5

3) cis-1,10-Hydrogen-1-quinolizidinol (10)

<u>molar conc.</u>	<u>mg/25 ml</u>	<u>Abs. area</u>	<u>E<sub>A</sub> x 10<sup>3</sup></u>
.00146	5.672	.849	5.8
.00073	12.5/25 of .00146	.492	6.7
.00059	10/25 of .00146	.325	5.5

Table 7

## Integrated Intensities of Bonded Hydroxyl Groups

1) trans-1,10-Hydrogen-1-quinolizidinol (11)

<u>molar conc.</u>	<u>mg/25 ml</u>	<u>Abs. area</u>	<u>E<sub>A</sub> x 10<sup>3</sup></u>
.00182	7.062	.685	3.76
.00138	5.368	.511	3.68
.00097	3.846	.346	3.57
.00073	10/25 of .00182	.288	3.94
.00039	10/25 of .00097	.134	3.44

## 2) Cholesterol

<u>molar conc.</u>	<u>mg/25 ml</u>	<u>Abs. area</u>	<u>E<sub>A</sub> x 10<sup>3</sup></u>
.00155	14.984	.551	3.56
.00096	9.362	.347	3.62
.00062	10/25 of .00155	.235	3.79
.00038	10/25 of .00086	.155	4.03

3)  $\beta$ -3,5-Dimethyl-2,6-diphenyl-4-piperidinol  
(40b)

<u>molar conc.</u>	<u>mg/25 ml</u>	<u>Abs. area</u>	<u>E<sub>A</sub> x 10<sup>3</sup></u>
.00127	8.904	.480	3.78
.00051	10/25 of .00127	.223	4.37

continued -

Table 7 cont'd

## 4) 3-Methyl-3-azabicyclo[3.3.1]nonan-9-ol (62)

<u>molar conc.</u>	<u>mg/25 ml</u>	<u>Abs. area</u>	<u>E<sub>A</sub> x 10<sup>3</sup></u>
.00135	5.244	.489	3.63
.00055	2.148	.210	3.78

## 5) 1,2,2,6,6-Pentamethyl-4-piperidinol (37)

<u>molar conc.</u>	<u>mg/25 ml</u>	<u>Abs. area</u>	<u>E<sub>A</sub> x 10<sup>3</sup></u>
.00185	7.935	.634	3.43
.00157	6.698	.587	3.74
.00127	5.413	.503	3.96
.00094	4.002	.375	3.99

## 6) 1,4-Dimethyl-2,6-diphenyl-4-piperidinol (41)

<u>molar conc.</u>	<u>mg/25 ml</u>	<u>Abs. area</u>	<u>E<sub>A</sub> x 10<sup>3</sup></u>
.00114	7.970	.442	3.87
.00088	6.186	.335	3.81
.00061	4.262	.227	3.72

## 7) 1-Methyl-2,6-diphenyl-4-piperidinol (39)

<u>molar conc.</u>	<u>mg/25 ml</u>	<u>Abs. area</u>	<u>E<sub>A</sub> x 10<sup>3</sup></u>
.00104	6.912	.385	3.71

Table 8

Percentage of Unbonded Hydroxyl and Conformational Free  
Energy Difference of 3- and 4- Piperidinols

<u>Piperidinol</u>		<u>Absorbance</u>	<u>Conc. (g/l)<sup>a</sup></u>	<u>% Unbonded OH</u>	<u>- <math>\Delta G^\circ</math> at 37° Kcal/Mole</u>	<u>-<math>\Delta G^b</math></u>
<u>3-Piperidinols</u>						
1-H	(28)	0.552	0.00148	60%	+0.25	+0.37
1-CH <sub>3</sub>	(3)	0.536	0.00143	57	+0.18	+0.25
1-CH <sub>2</sub> CH <sub>3</sub>	(29)	0.469	0.00125	50	0.00	+0.39
1-CH <sub>2</sub> Ph	(30)	0.496	0.00133	54	+0.10	
1-CH <sub>2</sub> Ph	(42)	0.161	0.00043	17	-0.98	
3-CH <sub>3</sub>						
1-CH <sub>2</sub> Ph	(43)	0.133	0.00036	14	-1.12	
3-CH <sub>2</sub> CH <sub>3</sub>						
<u>1,2,2,6,6-Pentamethyl-4-Piperidinols</u>						
4-CH <sub>3</sub>	(44)	0.453	0.00121	58	+0.20	
4-CH <sub>2</sub> CH <sub>3</sub>	(45)	0.234	0.00063	54	+0.10	

- a) Calculated from the molar absorptivity of model compounds using the following equation:

$$C = \frac{\text{Abs.}}{\epsilon \times \ell} \quad \text{where the molar absorptivity } (\epsilon) \text{ is } 3.74 \times 10^3 \text{ and the cell path length } (\ell) \text{ is } 10 \text{ cm.}$$

- b) The conformational free energy difference determined by nuclear magnetic resonance spectroscopy.



Table 9

AF/Ab Ratio and  $\Delta\nu_{\text{OH}}$  Shift of 1,2,2,6,6-Penta-  
methyl-4-piperidinols

<u>2,2,6,6-Tetramethyl- 4-piperidinol</u>	$\Delta\nu_{\text{OH}}$ <u>cm<sup>-1</sup></u>	<u>AF/Ab<sup>*</sup></u>
1-Methyl-4-phenyl	242	$\frac{380}{1145} = 0.33$
1-Methyl-4-ethyl	216	$\frac{340}{700} = 0.48$
1,4-Dimethyl	200	$\frac{292}{465} = 0.63$

\* AF/Ab data was determined from the transmission spectra obtained on the Perkin Elmer Model 337 equipped with scale expansion.

Table 10

## Infrared Hydroxyl Stretching Vibrations of Hindered Alcohols in Various Solvents

Compound	Solvent	Conc Molar	Infrared Bands cm <sup>-1</sup>		$\Delta V_{OH}$ cm <sup>-1</sup>
$\alpha$ -1,3,5-Trimethyl-2,6-diphenyl-4-piperidinol ( <u>49a</u> )	<u>n</u> -hexane <sup>a</sup>	ca 5 x 10 <sup>-3</sup>	3655	3615	40
	CCl <sub>4</sub>	5 x 10 <sup>-3</sup>	3652	3615	37
	CS <sub>2</sub>	5 x 10 <sup>-3</sup>	3635	3597	38
	CS <sub>2</sub> <sup>38</sup>	1 x 10 <sup>-3</sup>	3626	3588	
2,6-dimethyl cyclohexanol ( <u>52</u> )	<u>n</u> -hexane <sup>a</sup>	1 x 10 <sup>-2</sup> M	3650	3610(sh)	40
	CCl <sub>4</sub>	5 x 10 <sup>-3</sup> M	3652	3615	37
	CS <sub>2</sub>	5 x 10 <sup>-3</sup> M	3635	3602(sh)	33
1,2,2,6,6-pentamethyl-4-piperidinol ( <u>37</u> )	CCl <sub>4</sub>	5 x 10 <sup>-3</sup> M	3630	----	--
	CS <sub>2</sub>	5 x 10 <sup>-3</sup> M	3615	----	--

a) 1.0 mm NaCl optics used; all other runs were done in 1.0 cm. silica cells

Table 11

Areas of Hydroxyl Bands of 3 and 4-Piperidinols\*

<u>3-Piperidinol</u>	<u>mg/25 ml CCl<sub>4</sub></u>	<u>Conc. x 10<sup>+3</sup> M</u>	<u>AF/Ab</u>
Unsubstituted ( <u>28</u> )	6.126	2.45	$\frac{552}{782} = 0.71$
1-Methyl ( <u>3</u> )	7.514	2.50	$\frac{536}{1086} = 0.495$
1-Ethyl ( <u>29</u> )	13.428/41 ml	2.50	$\frac{469}{1296} = 0.36$
1-Benzyl ( <u>30</u> )	11.726	2.46	$\frac{496}{975} = 0.51$
1-Benzyl-3-methyl ( <u>42</u> )	12.832	2.49	$\frac{161}{1285} = 0.125$
1-Benzyl-3-ethyl ( <u>43</u> )	13.816	2.53	$\frac{133}{1693} = 0.079$
<u>1,2,2,6,6-Pentamethyl-4-piperidinol</u>			
4-Methyl ( <u>44</u> )	9.630	2.08	453
4-Ethyl ( <u>45</u> )	5.845	1.16	234

\* Spectra determined using the Beckman IR 12.

TABLE 12

LEAST MEANS SQUARE DETERMINATION OF THE  
PLOT OF DATA FROM TABLE 7

Unbonded Hydroxyl Absorbance (X)	Molar Conc. (Y)		
0.685000	0.00182	1.00000	
0.511000	0.00138	1.00000	
0.346000	0.00097	1.00000	
0.288000	0.00073	1.00000	
0.134000	0.00039	1.00000	
0.551000	0.00155	1.00000	
0.347000	0.00096	1.00000	
0.235000	0.00062	1.00000	
0.155000	0.00038	1.00000	
0.480000	0.00127	1.00000	
0.223000	0.00051	1.00000	
0.489000	0.00135	1.00000	
0.210000	0.00055	1.00000	
0.634000	0.00185	1.00000	
0.587000	0.00157	1.00000	
0.503000	0.00127	1.00000	
0.375000	0.00094	1.00000	
0.442000	1.00114	1.00000	
0.335000	0.00088	1.00000	
0.227000	0.00061	1.00000	
X=X	Y=Y	CALCY	DIF
0.685000	0.00182	0.00187	-0.00005
0.511000	0.00138	0.00138	-0.00000
0.346000	0.00097	0.00092	0.00005
0.288000	0.00073	0.00076	-0.00003
0.134000	0.00039	0.00033	0.00006
0.551000	0.00155	0.00149	0.00006
0.347000	0.00096	0.00092	0.00004
0.235000	0.00062	0.00061	0.00001
0.155000	0.00038	0.00039	-0.00001
0.480000	0.00127	0.00129	-0.00002
0.223000	0.00051	0.00058	-0.00007
0.489000	0.00135	0.00132	0.00003
0.210000	0.00055	0.00054	0.00001
0.634000	0.00185	0.00172	0.00013
0.587000	0.00157	0.00159	-0.00002
0.503000	0.00127	0.00136	-0.00009
0.375000	0.00094	0.00100	-0.00006
0.442000	0.00114	0.00119	-0.00005
0.335000	0.00088	0.00089	-0.00001
0.227000	0.00061	0.00059	0.00002

A = 0.4628E-04

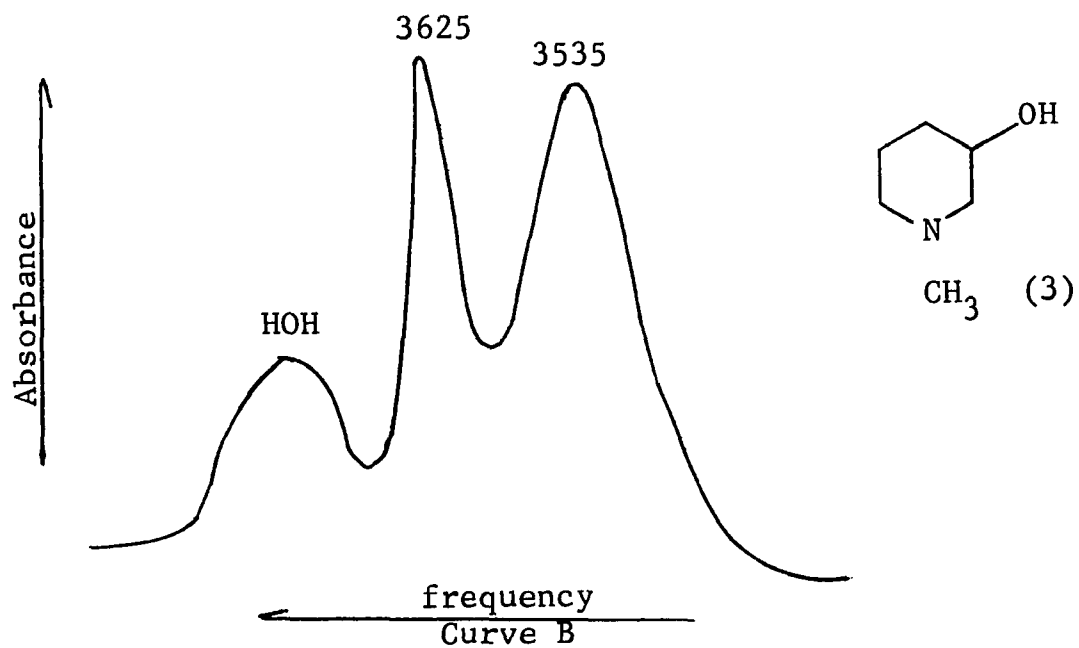
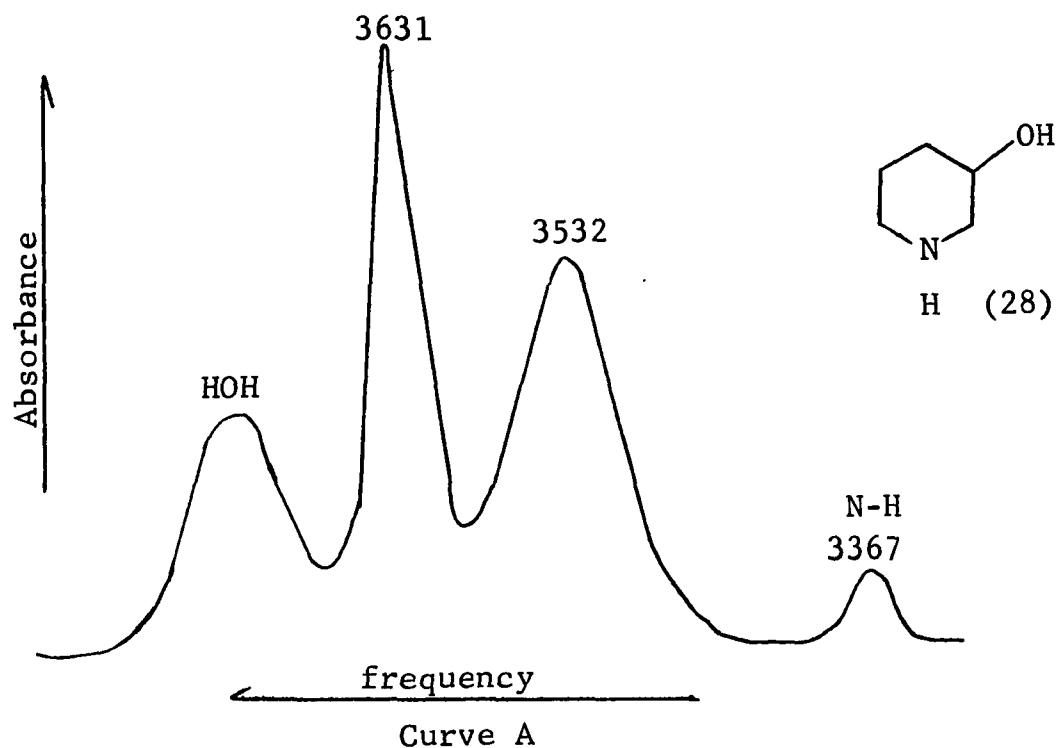
DEV.A = 0.3130E-04

DEV.Y = 0.532E-04

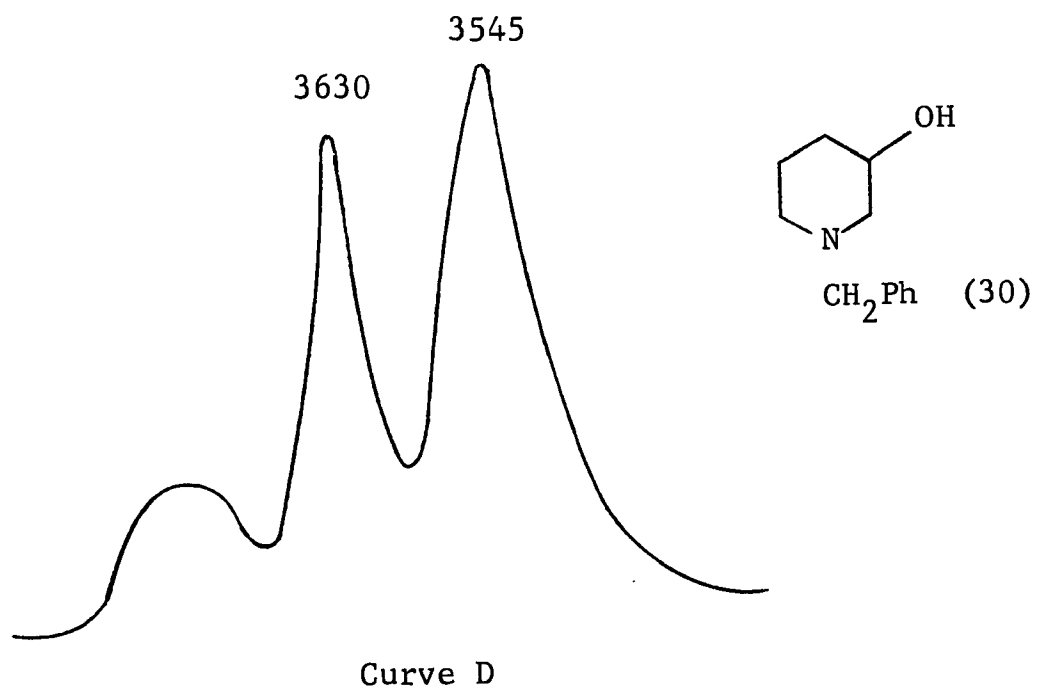
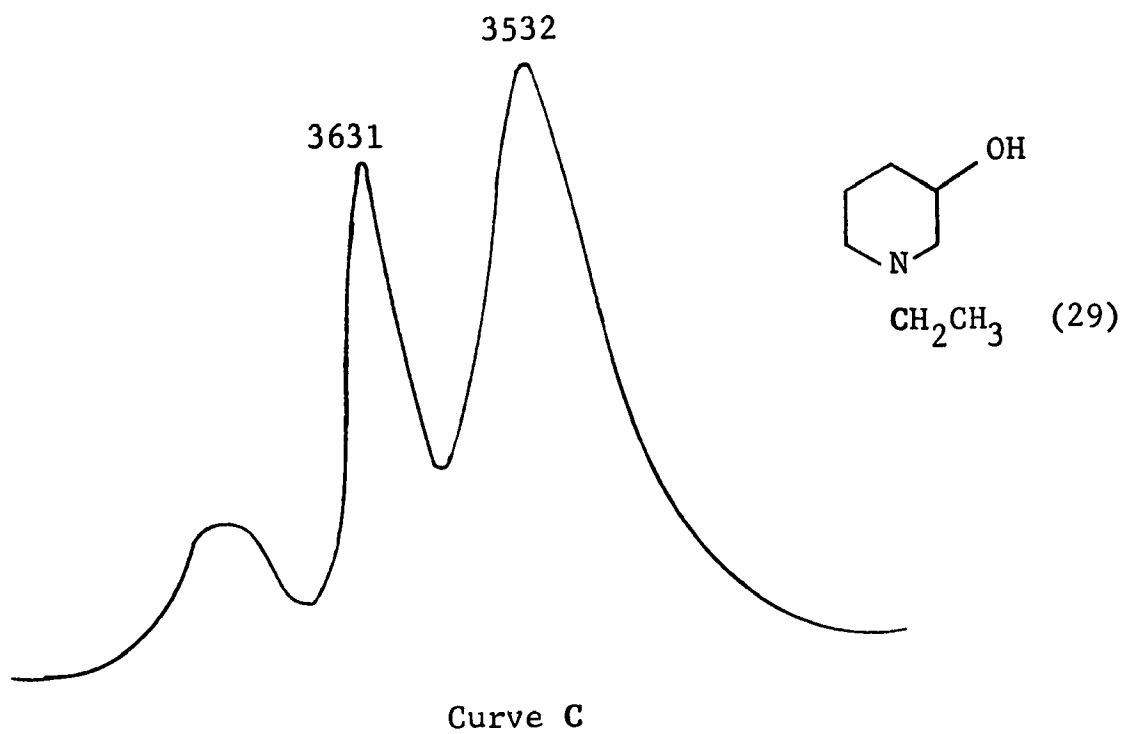
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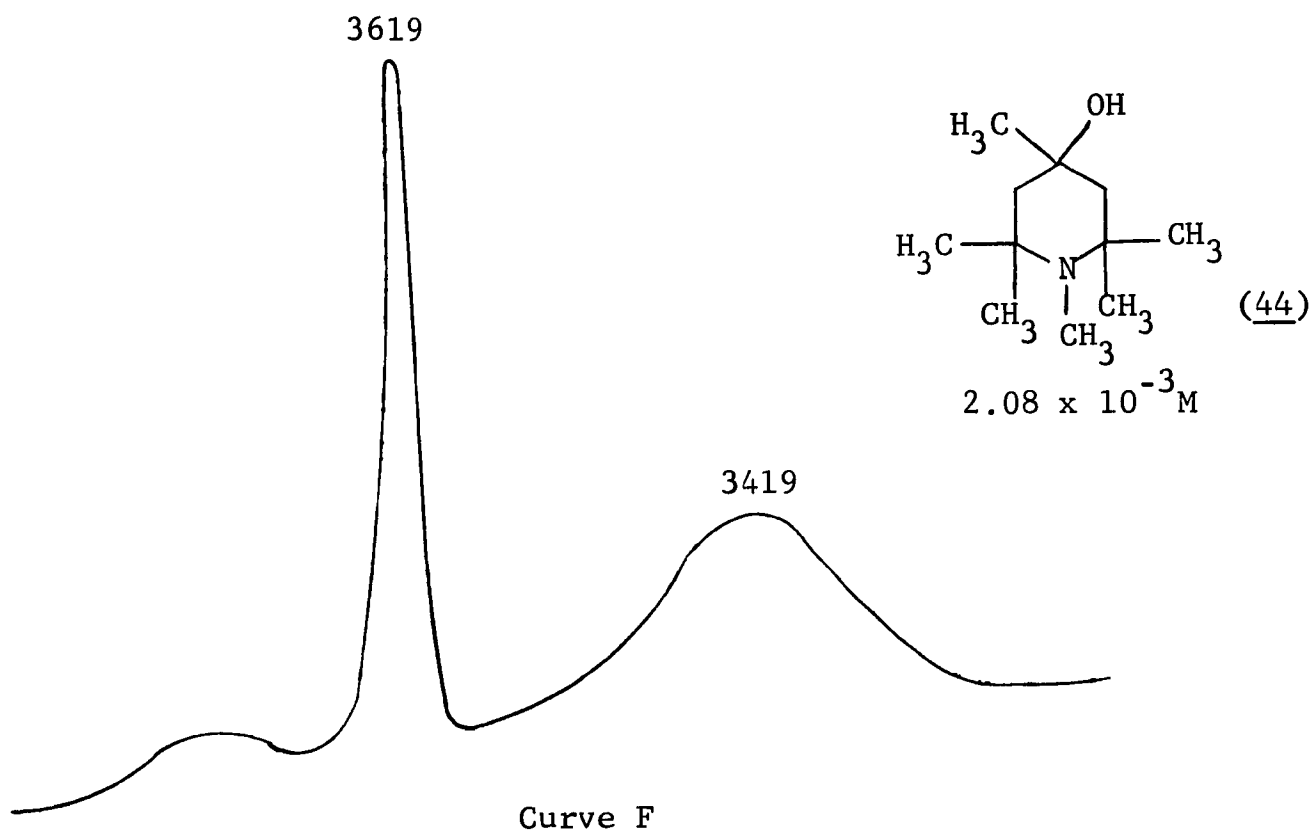
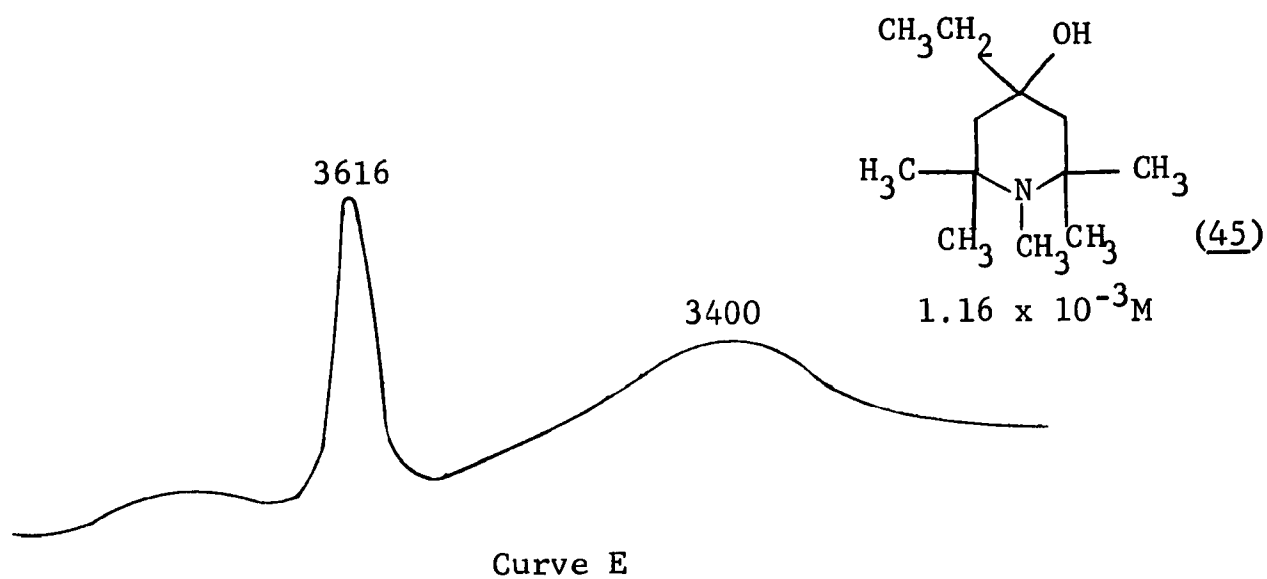
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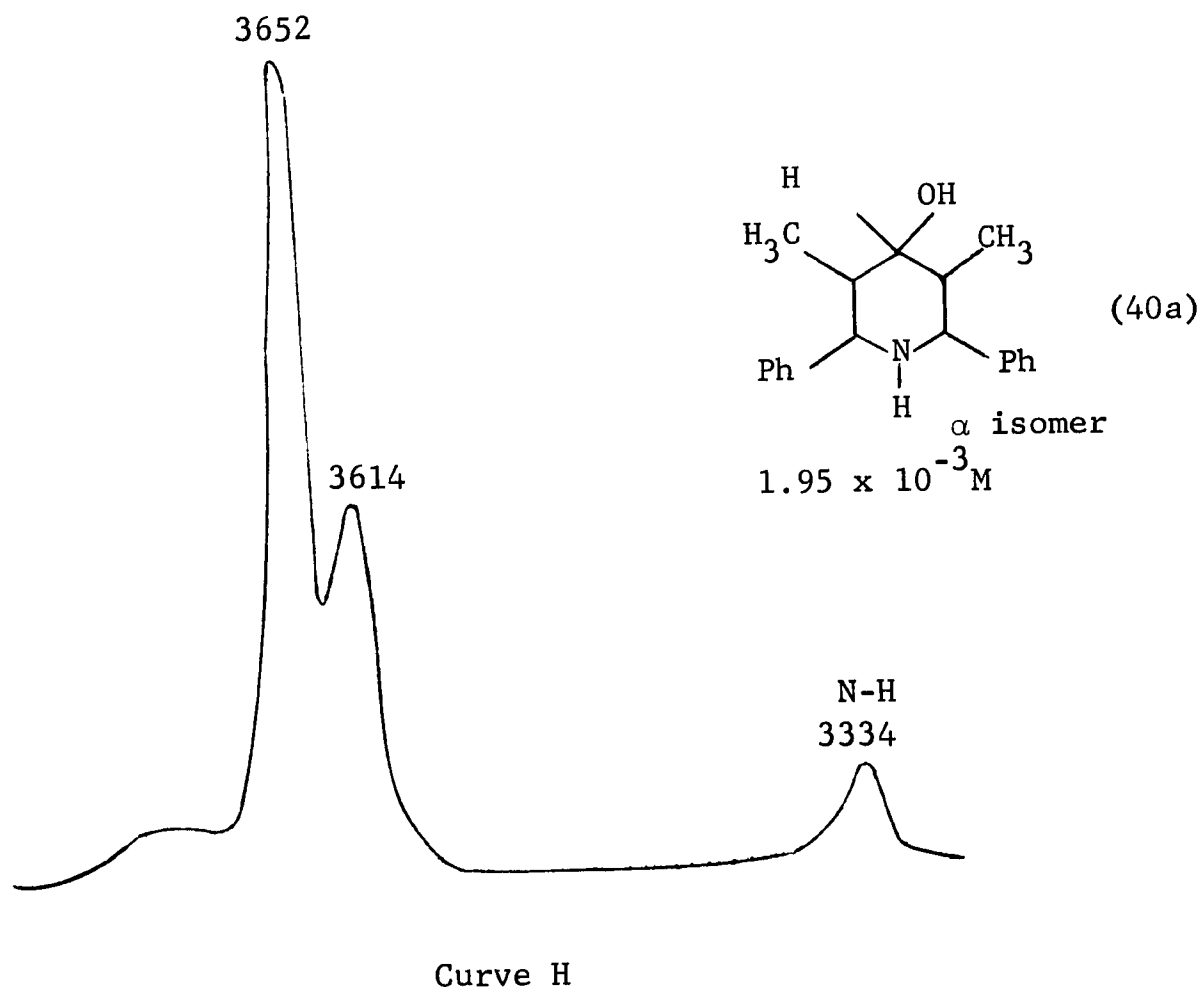
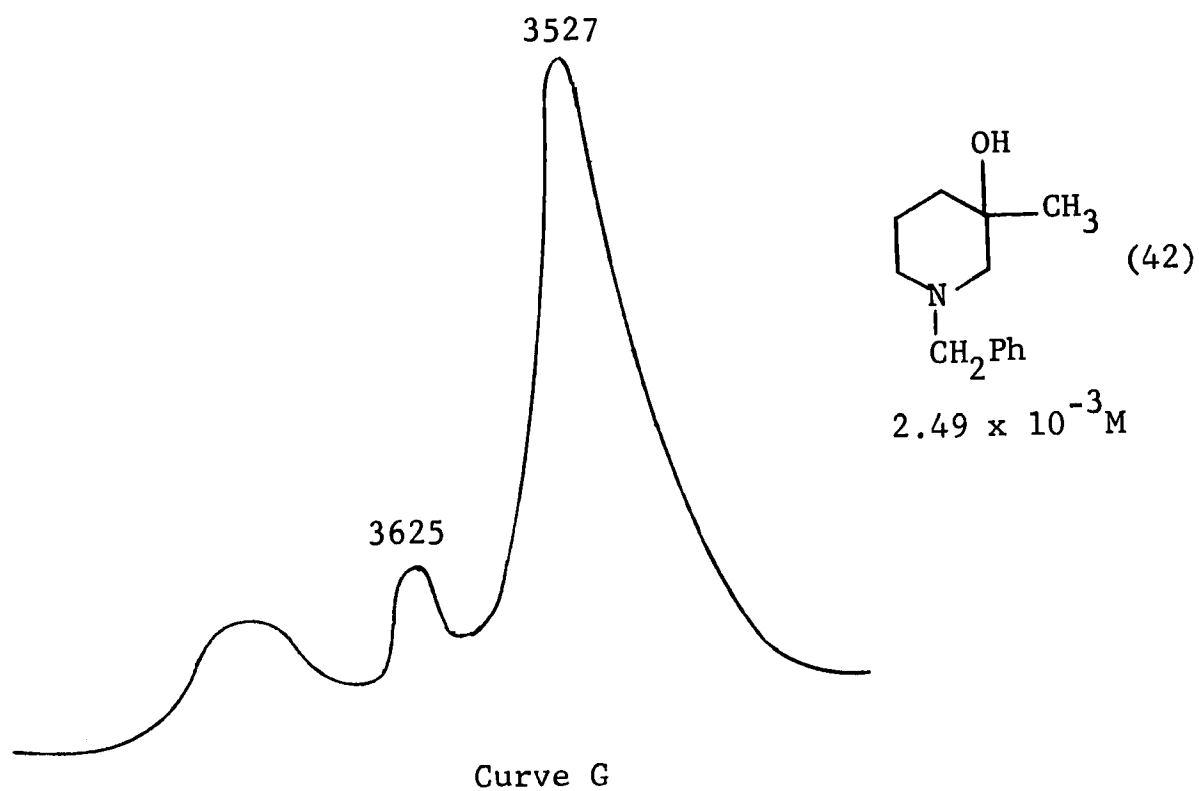
R = 0.9936

Infra-Red Spectra of Piperidinols in  
the Hydroxyl Stretching Region

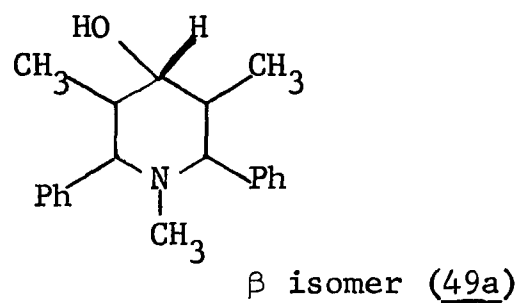
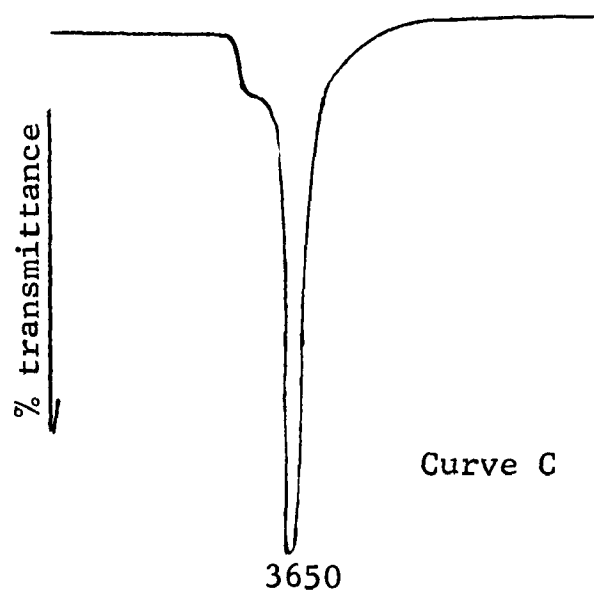
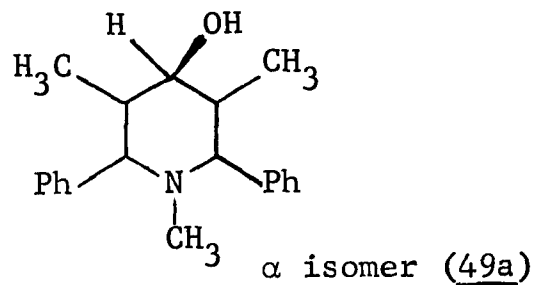
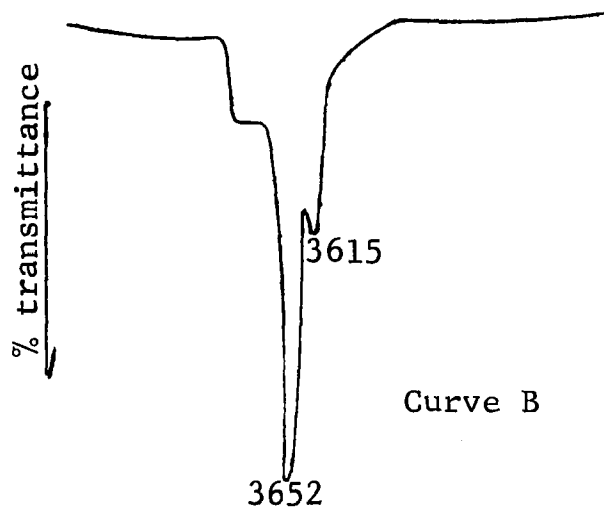
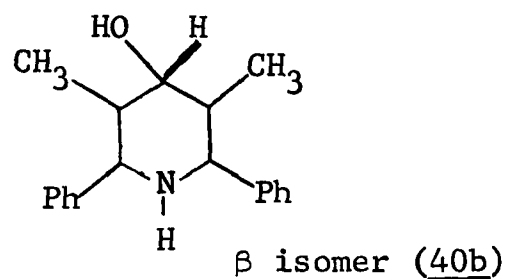
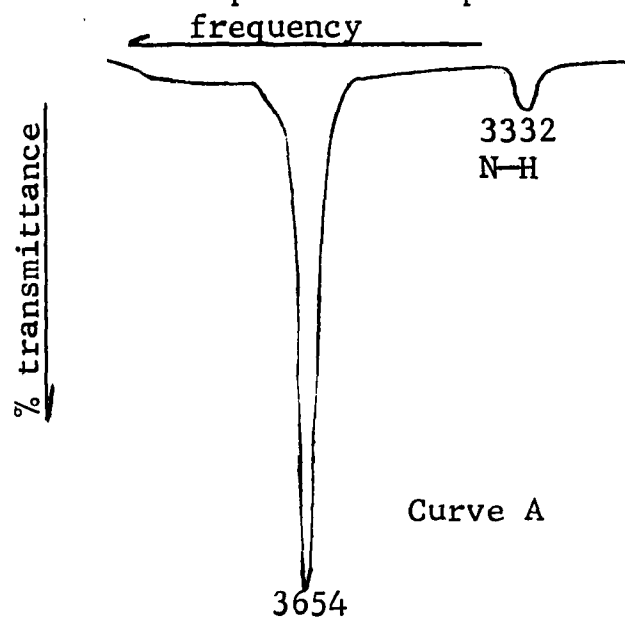
<sup>a</sup> These spectra were determined on the Beckman IR-12



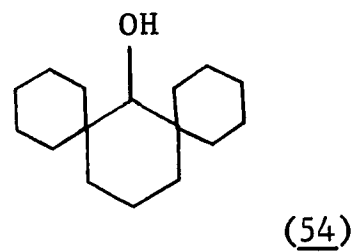
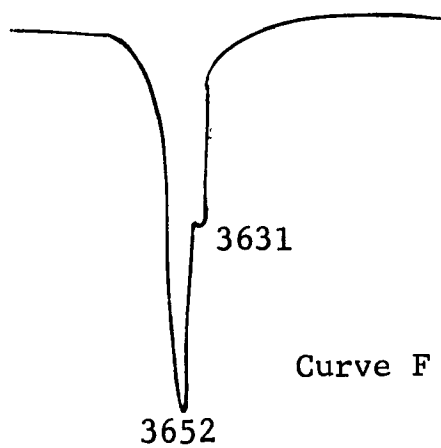
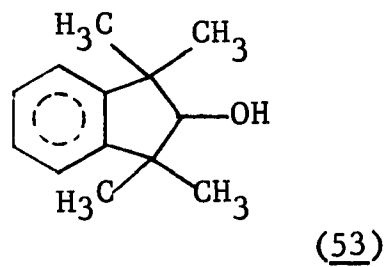
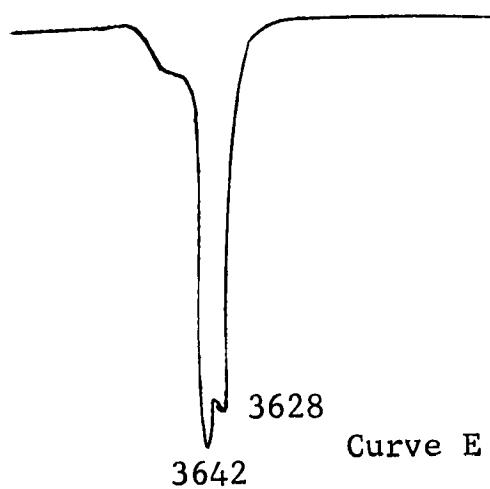
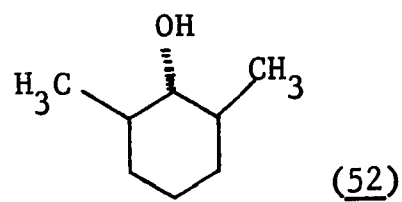
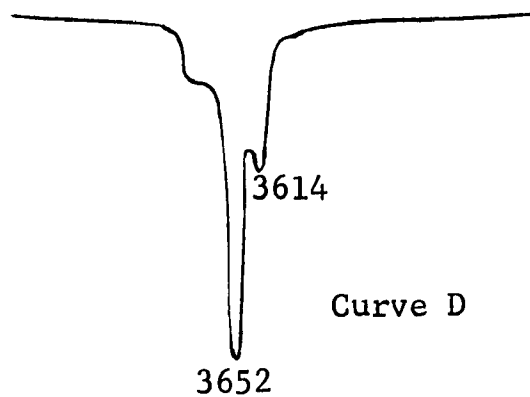


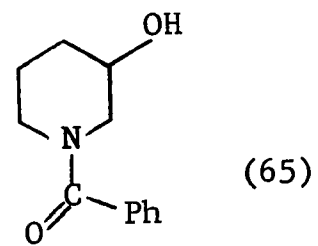
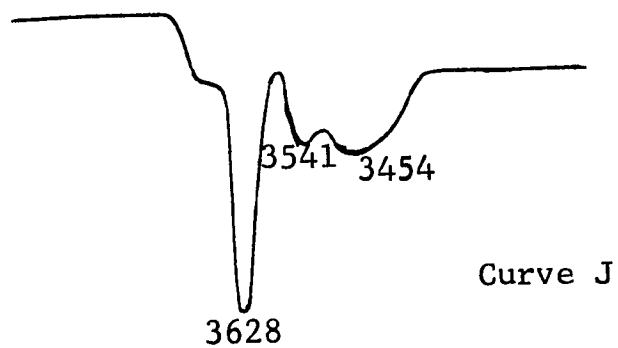
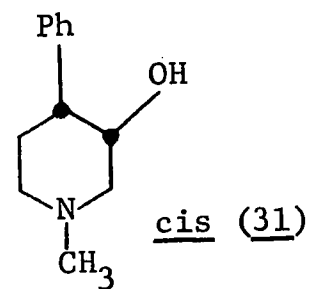
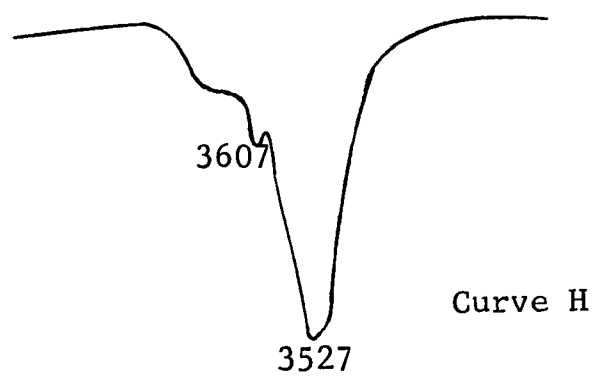
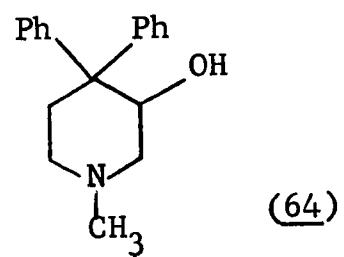
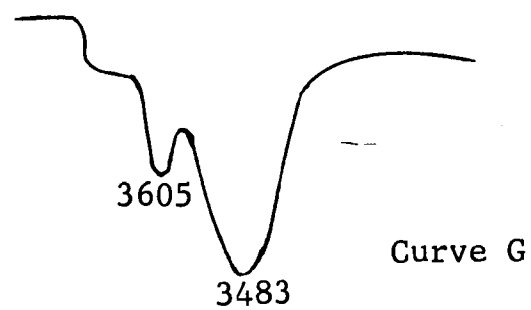


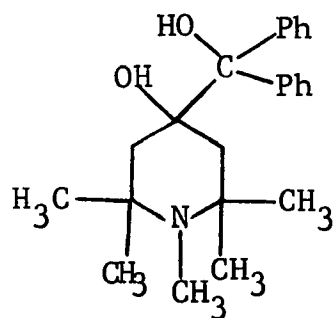
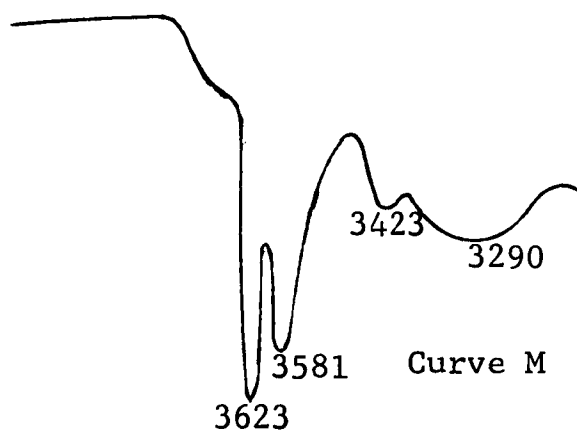
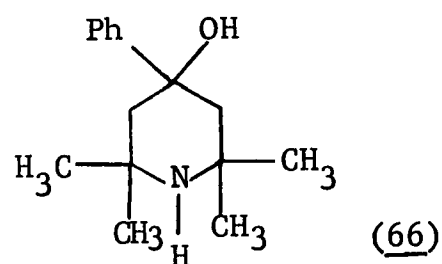
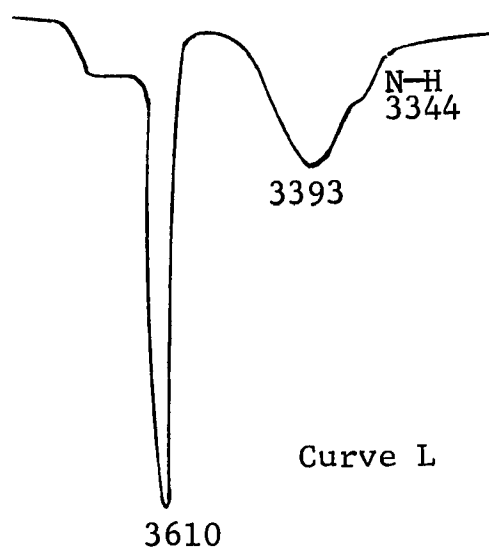
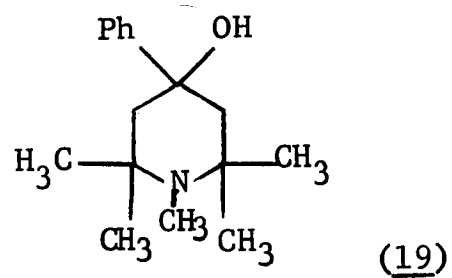
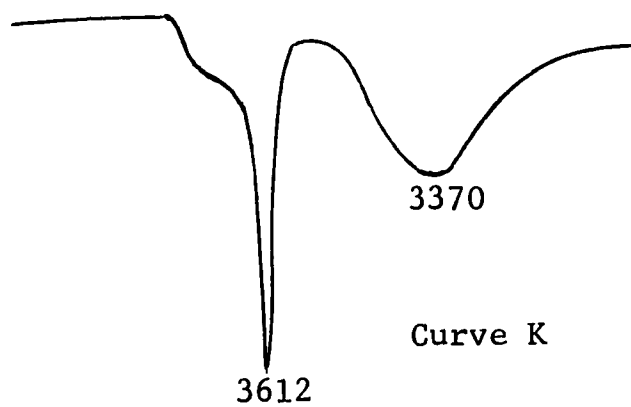


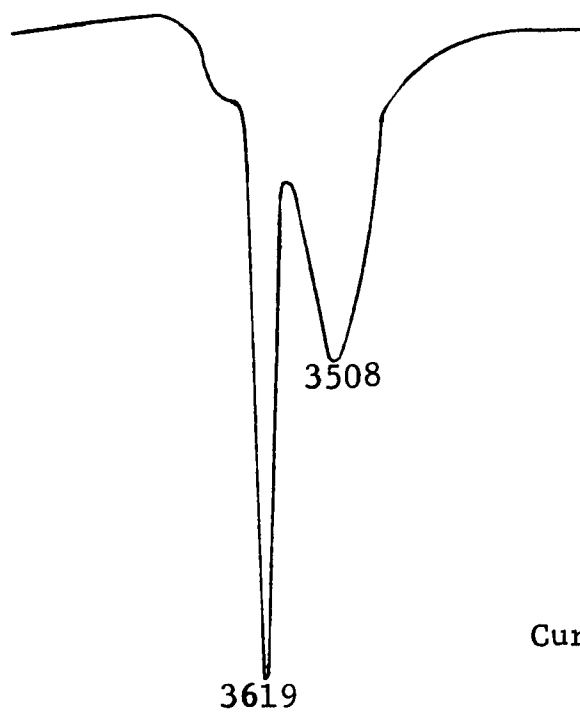
Infrared Spectra of Piperidinols in the Hydroxyl Stretching  
Region at  $5 \times 10^{-3}$  M Concentration

a) These spectra were determined on the Perkin-Elmer Model 337

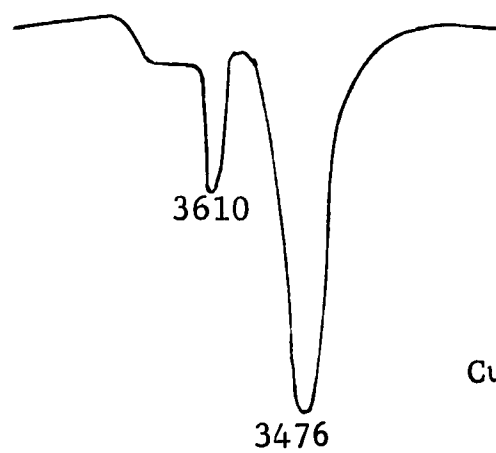
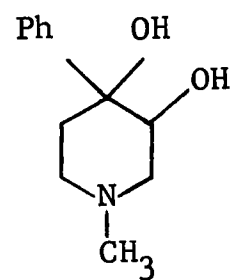








Curve N



Curve P

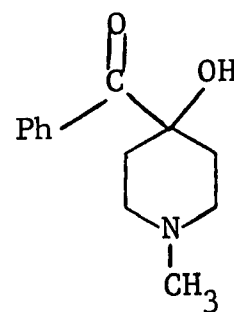


FIGURE VII

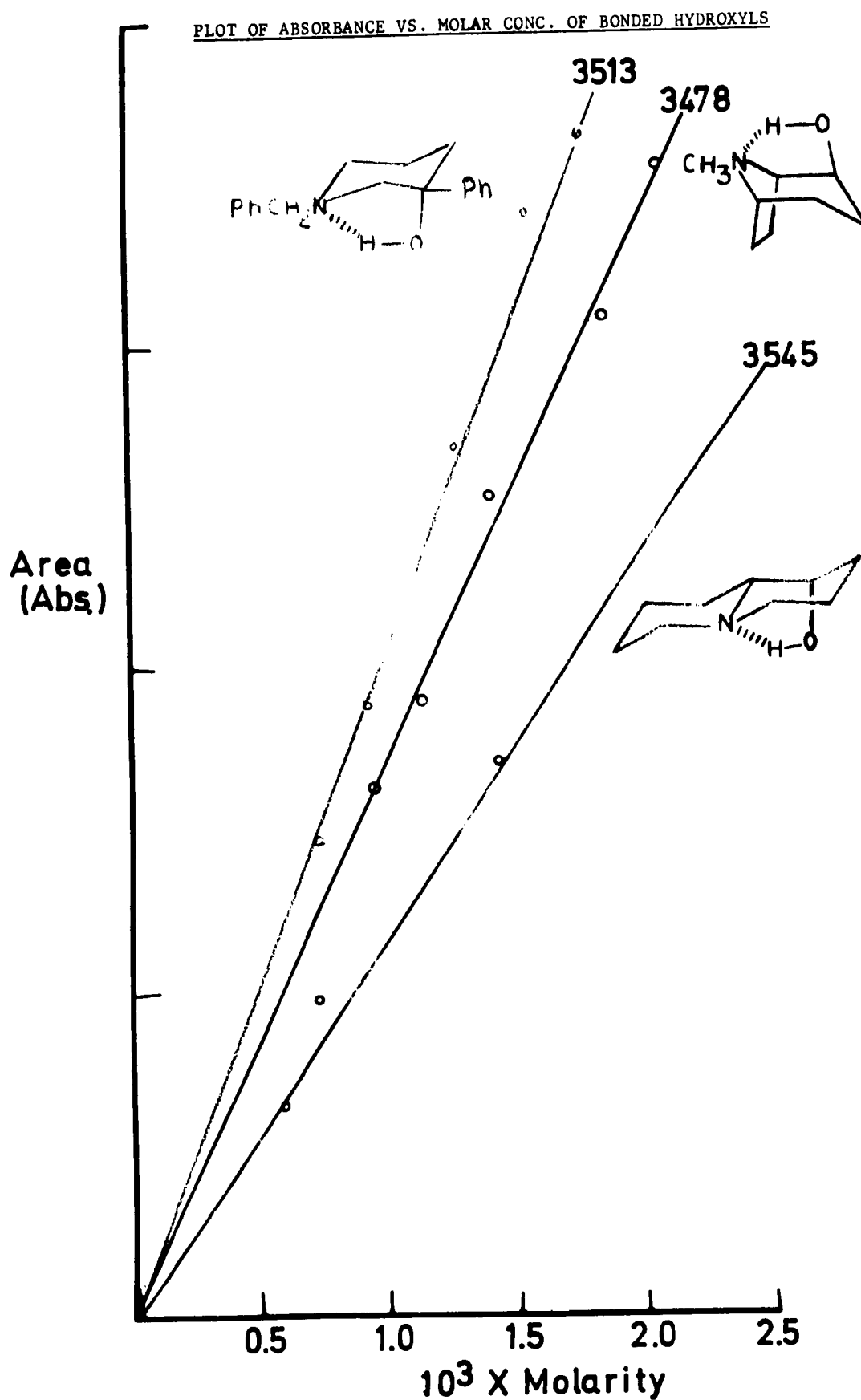
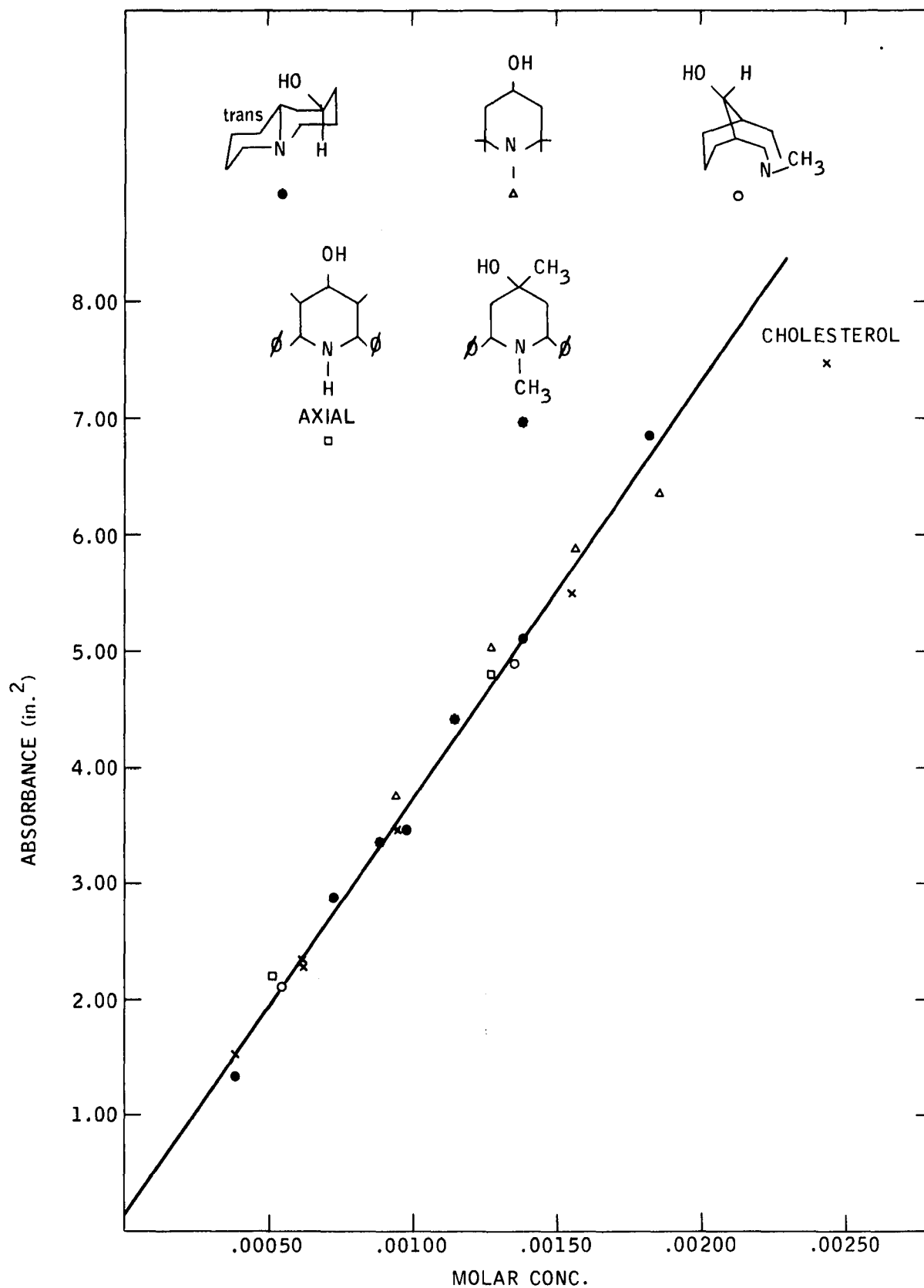
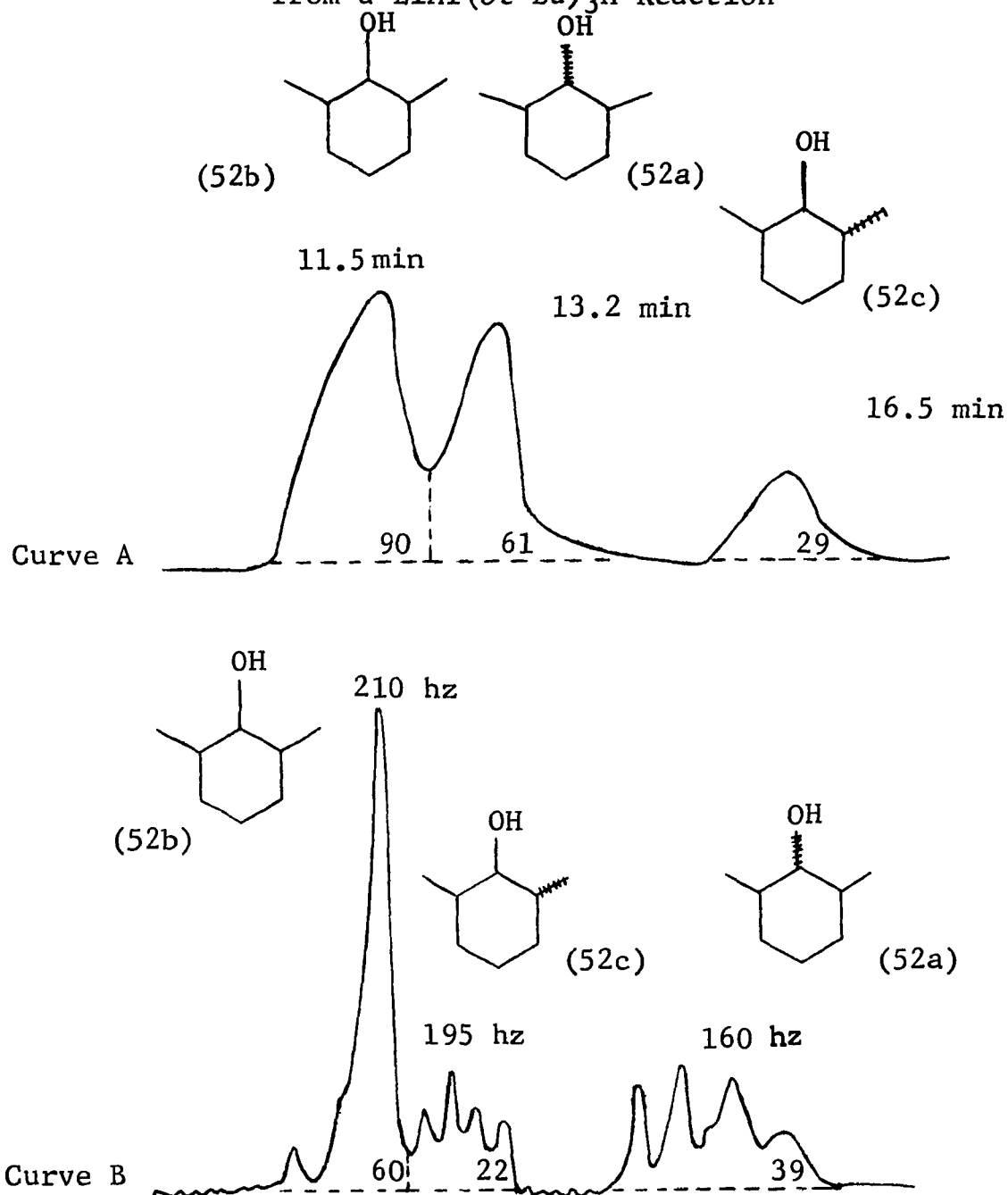


Figure 8

PLOT OF ABSORBANCE AREAS  
vs. MOLAR CONC. OF UNBONDED HYDROXYLS



Gas Chromatographic Analysis and NMR Spectrum of the  
Carbinol Protons of 2,6-Dimethylcyclohexanol  
from a  $\text{LiAl}(\text{Ot-Bu})_3\text{H}$  Reaction





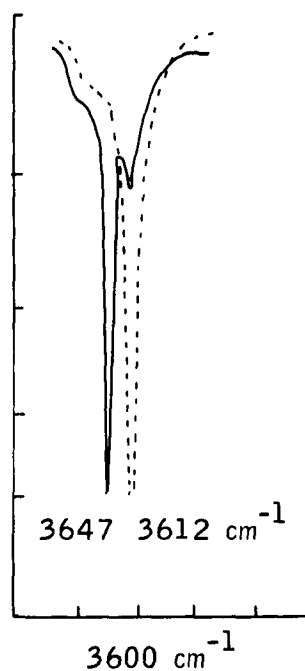
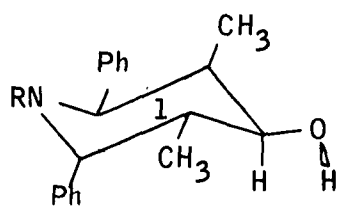
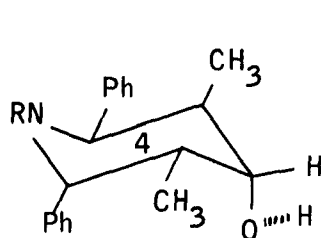
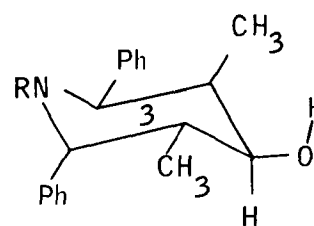
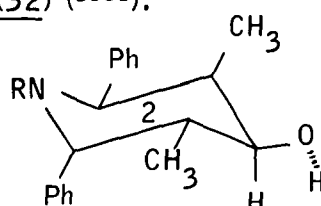


Figure 10  
THE INFRARED ABSORPTION DUE TO THE OH STRETCHING VIBRATION  
OF 49a (—) AND Trans-1METHYL-4-PHENYL-3-PIPERIDINOL  
(32) (----).



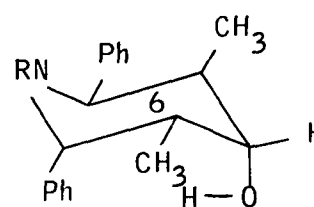
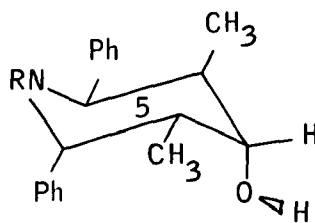
49a R = CH<sub>3</sub>

40a R = H



49b R = CH<sub>3</sub>

40b R = H



UNFAVORABLE

Figure 11  
THE POSSIBLE ROTATIONAL CONFORMATIONS  
OF THE HYDROXYL GROUPS IN 49 AND 40

## EXPERIMENTAL

### General

Melting Points. Melting points were determined using a Mel-Temp melting point apparatus and are corrected.

Elemental Analyses. Elemental analyses were determined by Weiler and Strauss Microanalytical Laboratory, Oxford, England, or using a F and M Model 185 carbon, hydrogen, and nitrogen analyzer. The microanalyses determined by Weiler and Strauss are indicated by Found<sup>ws</sup>; those determined using the F and M are indicated by Found<sup>fm</sup> and are the average of two or more runs.

Gas Chromatographic Data. The gas chromatographic analyses were determined using a Perkin-Elmer Model 154 Vapor Fractometer or with an Aerograph Autoprep Model A-700 using helium as the carrier gas. Mixtures were analyzed using a 2 m. column of carbowax 20M chromosorb W unless otherwise stated.

Nuclear Magnetic Resonance Spectra. The nuclear magnetic resonance spectra were determined using a Varian Model A-60 Spectrometer. Unless otherwise stated chemical shifts are reported as tau values from TMS as an internal standard. Solvents and temperature are indicated with each spectrum reproduced in the Appendix. The coupling constants of the carbinol protons were measured from curves determined at 100 Hz SCAN. Reproducibility of measured spacings of  $\pm 0.05$  Hz was possible. The presentation of the nmr data is given as follows: NMR Spectrum: (solvent): chemical shift from TMS (splitting pattern, no. of protons, coupling constant, peak

assignment). An example is NMR Spectrum: ( $\text{CCl}_4$ ): 3.98 (t, 2,  $J = 6$  Hz,  $\text{CH}_2\text{OAc}$ ). In nmr descriptions, s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet.

Infrared Spectra in Percent Transmission. The infrared spectra were determined using a Perkin-Elmer Model 337 grating infrared spectrophotometer equipped with scale expansion using solutions in carbon tetrachloride at dilutions of  $5 \times 10^{-3}$  M and with silica cells of path length of 1.00 cm. (see Figure VI). The frequencies of the absorption bands were determined by calibration against the absorption of polystyrene at  $2850 \text{ cm}^{-1}$ .

Determination of Relative Area of Absorption Bands of Unbonded and Intramolecularly Hydrogen-Bonded Hydroxyl Groups.

The solutions of the hydroxyl-containing compounds were prepared in carbon tetrachloride at approximately  $2.5 \times 10^{-3}$  molar concentrations. The compounds were weighed on a Cahn Ratio Electrobalance (Model G) in small aluminum boats which were placed directly into the volumetric flask before dilution. The spectra between  $3900$  and  $3300 \text{ cm}^{-1}$  were determined using a Beckman IR 12 infrared grating spectrophotometer. The settings of the Beckman IR 12 were as follows: gears, 36 left, 90 right; glower current 0.60 amps; double beam, selected slit width of 1.3 mm at  $3300 \text{ cm}^{-1}$ ; Gain, 0.35, Period 2, 0-1 Absorbance, Speed,  $40 \text{ cm}^{-1}/\text{min}$ . The solution was contained in a 10.0 cm Beckman fused silica cell and was balanced in the reference beam with a matched cell containing solvent. The cell holders used were the Cary 15 Ultraviolet Spectrometer cell holders. The curves were plotted in reciprocal centimeters and over this limited range the curves were linear. The baseline was connected at both ends of the spectra. The areas were

measured with a K and E planimeter in which 100 units equals 1 square inch, an illustration of this method was the solution of 49.6 mole percentage 1,2,2,6,6-pentamethyl-4-piperidinol (37), unbonded OH, and 50.4 mole percentage 1-benzyl-3-phenyl-3-piperidinol (38) bonded OH. The absorption of any water present in the sample appears as a band in the spectrum near  $3700\text{ cm}^{-1}$ . The band is resolved from the unbonded hydroxyl peak and therefore does not contribute any area to the unbonded OH peak.

1-Benzyl-3-piperidinol (30). A solution of 17.1 g. (0.100 mole) of benzyl bromide in 50 ml. of absolute ethanol was added dropwise to a stirred solution of 5.0 g. (0.050 mole) of 3-piperidinol (28) (Aldrich Chemical Co.) dissolved in 100 ml. of absolute ethanol.<sup>47</sup> The reaction mixture was allowed to stir at reflux temperature for 20 hrs. The mixture cooled and then 500 ml. of ether was added causing the hydrobromide to precipitate as an oil. The solvent mixture was decanted, and 50 ml. of aqueous 2N sodium carbonate solution was added to the remaining oil. The water layer was extracted twice with 100 ml. of ether. The combined organic layers were dried over magnesium sulfate and concentrated to yield 5.1 g. (54%) of 1-benzyl-3-piperidinol as a reddish oil. The reddish oil (3.1 g.) was distilled under reduced pressure to yield 2.6 g. of a colorless viscous liquid, b. p.  $171-3^{\circ}$  at 18 mm. pressure; lit.<sup>42</sup> b.p.  $107^{\circ}$  at 0.1 mm. pressure.

Infrared Spectrum: A 0.00246 molar solution of 1-benzyl-3-piperidinol (30) in carbon tetrachloride solution gave a free hydroxyl stretching vibration at  $3630\text{ cm}^{-1}$  and a bonded hydroxyl stretching vibration at  $3545\text{ cm}^{-1}$  in which the  $\Delta\nu_{\text{OH}}$  shift was  $85\text{ cm}^{-1}$  (see Figure V, Curve D).

NMR Spectrum: (pyridine, No. 3215): 2.74 (s, 5,  $\text{C}_6\text{H}_5$ ),

4.77 (s,1, OH), 6.25 (m,1, CH-OH), 6.60 (s,2, -CH<sub>2</sub>Ph), 7.05 (q, 2,  $\underline{J}$  = 11 Hz), 7.50-8.50 (m), (see Figure IV, Curve B for the carbinol proton of 30).

1-Benzyl-3-methyl-3-piperidinol (42). A solution of 11.2 g. (0.079 mole) of methyl iodide in 50 ml. of ether was added to 3.8 g. (0.158 mole) of magnesium powder. The reaction mixture was stirred for 3 hrs. at room temperature and an ether solution of 5.0 g. (0.026 mole) of 1-benzyl-3-piperidone<sup>42</sup> (69) was added dropwise. Stirring was maintained at room temperature for 4 hrs. The reaction mixture was worked up according to the procedure for the preparation of 1,2,2,4,6,6-hexamethyl-4-piperidinol (44) to yield 2.8 g. of a reddish oil. Distillation of the reddish oil yielded 1.0 g. of 1-benzyl-3-methyl-3-piperidinol (42) as a pale yellow liquid, b.p. 165-169° at 21 mm. pressure.

Anal. Calcd. for C<sub>13</sub>H<sub>19</sub>NO: C, 76.05; H, 9.33; N, 6.83. Found<sup>FM</sup>: C, 76.49; H, 8.99; N, 6.81.

Gas Chromatographic Analysis. Using a 1 meter Carbowax 20M chromosorb W column at 163° and at 19 psi, the reddish oil obtained before distillation was shown to consist of a mixture of 10.4% 1-benzyl-3-piperidone (69) (5.0 min. retention time), compared with an authentic sample<sup>42</sup>, and 89.6% 1-benzyl-3-methyl-3-piperidinol (42), 3.2 min. retention time.

Infrared Spectrum: A 0.00249 molar solution of 1-benzyl-3-methyl-3-piperidinol (42) in carbon tetrachloride solution showed a hydroxyl stretching vibration at 3625 cm<sup>-1</sup> and a bonded hydroxyl stretching vibration at 3527 cm<sup>-1</sup>, in which the  $\Delta V_{OH}$  shift was 98 cm<sup>-1</sup> (see Figure V, Curve G).

NMR Spectrum: (neat, No. 3656): 2.78 (s,5, C<sub>6</sub>H<sub>5</sub>-), 6.00 (s,1, OH), 6.60 (s,2, -CH<sub>2</sub>Ph), 7.58 (d,2,  $\underline{J}$  = 11 Hz),

8.02 (d,2, $\underline{J}$  = 11 Hz), 8.56 (m), 8.88 (s,3,  $\text{-CH}_3$ ) (see Figure XXI, Curve B for the complete spectrum of 42).

1-Benzyl-3-ethyl-3-piperidinol (43). A solution of 8.2 g (0.079 mole) of ethyl bromide in 50 ml. of ether was added to 1.9 g. (0.079 mole) of magnesium turnings. After all the magnesium turnings had undergone reaction, an ether solution of 5.0 g. (0.026 mole) of 1-benzyl-3-piperidone<sup>42</sup> (69) was added. Stirring was maintained at room temperature for 5 hrs. The reaction mixture was worked up according to the procedure for the preparation of 1,2,2,4,6,6-hexamethyl-4-piperidinol (44) to yield 3.2 g. (55%) of a red oil. Distillation of 1.5 g. of the red oil gave 0.9 g. of 1-benzyl-3-ethyl-3-piperidinol (43) as a pale yellow liquid, b.p. 171-4° at 18 mm. pressure.

Anal. Calcd. for  $\text{C}_{14}\text{H}_{21}\text{NO}$ : C, 76.66; H, 9.65; N, 6.39.  
Found<sup>FM</sup>: C, 76.14; H, 9.06; N, 6.46.

Gas Chromatographic Analysis. The liquid was homogeneous to gas chromatographic analysis with a retention time of 3.2 minutes using a 1 meter Carbowax 20M chromosorb W column at 165° and 15 psi.

Infrared Spectrum: A  $5 \times 10^{-3}$  molar solution of 1-benzyl-3-ethyl-3-piperidinol (43) in carbon tetrachloride solution showed a hydroxyl stretching vibration at  $3628 \text{ cm}^{-1}$  and a bonded hydroxyl stretching vibration at  $3531 \text{ cm}^{-1}$ , in which the  $\Delta\nu_{\text{OH}}$  shift was  $97 \text{ cm}^{-1}$ .

NMR Spectrum: (neat, No. 3658): 2.79 (s,5,  $\text{C}_6\text{H}_5\text{-}$ ), 6.59 (s,2,  $\text{-CH}_2\text{Ph}$ ), 7.53 (d,2, $\underline{J}$  = 11Hz), 8.08 (d,2, $\underline{J}$  = 11 Hz), 8.56 (q,2, $\underline{J}$  = 7 Hz,  $\text{-CH}_2\text{CH}_3$ ), 9.13 (t,3, $\underline{J}$  = 7.5 Hz,  $\text{-CH}_2\text{CH}_3$ ), (see Figure XII, Curve C for the complete spectrum of 43).

1-Benzyl-3-phenyl-3-piperidinol (38). A solution of 24.8 g. (0.158 mole) of bromobenzene in 100 ml. of ether was added dropwise to a suspension of 22 g. (0.316 mole) of freshly cut lithium ribbon in 25 ml. of ether, and the reaction was stirred for 3 hrs. at room temperature. A solution of 7.0 g. (.037 mole) of 1-benzyl-3-piperidone<sup>42</sup> (69) in 50 ml. of ether was added over a period of 0.5 hr. The reaction mixture was allowed to stir at room temperature for 6 hrs. The reaction was hydrolyzed and worked up according to the procedure of Lyle<sup>15</sup> to yield 8.0 g. (82%) of orange-yellow solid, m.p. 70-73.5°. Recrystallization of the orange-yellow solid from n-heptane gave 4.5 g. (46%) of 1-benzyl-3-phenyl-3-piperidinol (38) as pale yellow crystals, m.p. 68-71°.

Anal. Calc. for  $C_{18}H_{21}NO$ : C, 80.90; H, 7.87; N, 5.24. Found<sup>ws</sup>: C, 81.25; H, 7.88; N, 5.04.

Infrared Spectrum: A 0.005 molar solution of 1-benzyl-3-phenyl-3-piperidinol (38) in carbon tetrachloride solution showed only a bonded hydroxyl stretching vibration at  $3513\text{ cm}^{-1}$ .

NMR Spectrum: ( $CCl_4$ , No. 1574): 2.79 (m, 10,  $-2C_6H_5$ ), 6.42 (s, 1, OH), 6.53 (s, 2,  $-CH_2Ph$ ), 7.33 (d, 2,  $J = 11\text{ Hz}$ ), 7.77 (d, 2,  $J = 11\text{ Hz}$ ), 8.27 (m, 2) (see Figure XII, Curve D for the complete spectrum of 38).

1-Methyl-3-acetoxy-piperidine (33). To a solution of 1.5 g. of sodium acetate dissolved in 30 ml. of acetic anhydride was added 7.0 g. (0.061 mole) of 1-methyl-3-piperidinol (3).<sup>42</sup> The reaction mixture was heated at 100° for 11 hrs. After cooling, the reaction mixture was poured into 100 ml. of distilled water and carefully neutralized with potassium carbonate. The aqueous layer was extracted three times with 100 ml. of ether. The combined organic layers were dried

over anhydrous potassium carbonate and concentrated to give 5.6 g. (58.5%) of an orange viscous liquid. The product was purified as the hydrobromide salt. The hydrobromide was prepared by bubbling hydrogen bromide gas into an acetone solution of 1-methyl-3-acetoxy-piperidine (33), yielding a white solid. Recrystallization of the white solid from 95% ethanol gave 1-methyl-3-acetoxy-piperidine hydrobromide, m.p. 108-111° as a white powder. The free base (33) was obtained by dissolving the hydrobromide in a minimum amount of water, basifying with potassium carbonate and extracting the aqueous layer three times with 25 ml. of ether. The combined organic layers were dried over anhydrous potassium carbonate and concentrated to give 1-methyl-3-acetoxy-piperidine (33) as a colorless viscous liquid.

Base: Anal. Calcd. for  $C_8H_{15}NO_2$ : C, 61.12; H, 9.62; N, 8.91. Found<sup>ws</sup>: C, 61.00; H, 9.50; N, 8.74. Hydrobromide: Anal. Calcd. for  $C_8H_{16}NO_2Br$ : C, 40.33; H, 6.72; N, 5.88. Found<sup>ws</sup>: C, 40.15; H, 6.97; N, 5.84.

NMR Spectrum: Base (neat, No. 1856): 5.42 (m, 1, -CH-OH), 7.28 (q, 2,  $J = 11$  Hz), 7.97 (s, 3, N-CH<sub>3</sub>), 8.21 (s, 3, -COCH<sub>3</sub>), 8.47 (m), (see Figure XII, Curve E for the complete spectrum of 33).

1,2,2,6,6-Pentamethyl-4-piperidone (70). The reaction of 100 g. (0.73 mole) of recrystallized phorone with 56.3 g. of 40% methylamine solution according to the procedure of R. R. Chauvette<sup>48</sup> gave 43.7 g. (28%) of 1,2,2,6,6-pentamethyl-4-piperidone, b. p. 88-91° at about 15 mm pressure; lit.<sup>48</sup>, b.p. 98° at 21 mm).

Gas Chromatographic Analysis. Using a 2 meter Carbowas 20M on chromosorb W column at 160° and 10 psi, the 1,2,2,6,6-pentamethyl-4-piperidone had a retention time of 3.0 minutes. Traces of phorone were present with a retention



time of 1.8 minutes.

NMR Spectrum: (neat, No. 796): 7.68 (s,4), 7.72 (s,3, N-CH<sub>3</sub>), 8.90 (s,12, -CH<sub>3</sub>).

1,2,2,4,6,6-Hexamethyl-4-piperidinol (44). A solution of approximately 0.0755 moles of methyl magnesium bromide was prepared by bubbling methyl bromide into a suspension of 1.8 g. (0.0755 mole) of magnesium turnings in 75 ml. of anhydrous ether. After all the magnesium turnings had undergone reaction, an ether solution of 5.0 g. (0.029 mole) of 1,2,2,6,6-pentamethyl-4-piperidone (70) was added. Stirring was maintained at room temperature for 4 hrs. The reaction mixture was hydrolyzed with a saturated ammonium chloride solution and allowed to stir for 0.5 hr. The magnesium salts were removed by filtration, and the water layer was drawn off and extracted twice with 100 ml. portions of ether. The combined ether layers were dried over potassium carbonate and evaporated to yield 3.5 g. of a dark oil. The oil was taken up in an equal volume of n-heptane, and on standing, a white solid separated. Recrystallization of the solid from n-heptane gave 2.0 g. (38%) of 1,2,2,4,6,6-hexamethyl-4-piperidinol (44) as white needles, m.p. 89-90.5°.

Anal. Calcd. for  $C_{11}H_{23}NO$ : C, 71.30; H, 12.51; N, 7.56. Found<sup>WS</sup>: C, 71.18; H, 12.31; N, 7.40.

Infrared Spectrum: A 0.00208 molar solution of 1,2,2,4,6,6-hexamethyl-4-piperidinol (44) in carbon tetrachloride solution showed an unbonded hydroxyl stretching vibration at  $3619\text{ cm}^{-1}$  and a bonded hydroxyl stretching vibration at  $3419\text{ cm}^{-1}$  in which the  $\Delta V_{OH}$  shift was  $200\text{ cm}^{-1}$  (see Figure V, Curve F).

NMR Spectrum: ( $CCl_3$ , No. 1552): 7.39 (s,1, -OH),

7.73 (s,3, N-CH<sub>3</sub>), 8.39 (s,4), 8.78 (s,6, -2CH<sub>3</sub>), 8.86 (s,3, -CH<sub>3</sub>), 8.92 (s,6, -2CH<sub>3</sub>), (see Figure XII, Curve F for the complete spectrum of 44).

1,2,2,6,6-Pentamethyl-4-ethyl-4-piperidinol (45).

A solution of 7.1 g. (0.0675 mole) of ethyl bromide in 75 ml. of ether was added to 1.6 g. (0.0675 mole) of magnesium turnings. After all the magnesium had undergone reaction, an ether solution of 5.0 g. (0.029 mole) of 1,2,2,6,6-pentamethyl-4-piperidone was added. Stirring was maintained at room temperature for 3 hr. The reaction mixture was worked up according to the procedure for the preparation of 1,2,2,4,6,6-hexamethyl-4-piperidinol (44) to yield after recrystallization with n-heptane 1.0 g. (17%) of 1,2,2,6,6-pentamethyl-4-ethyl-4-piperidinol (45) as white needles, m.p. 73-76°.

Anal. Calcd. for C<sub>12</sub>H<sub>25</sub>NO: C, 72.30; H, 12.65; N, 7.03. Found<sup>ws</sup>: C, 72.43; H, 12.72; N, 6.80.

Infrared Spectrum: A 0.00116 molar solution of 1,2,2,6,6-pentamethyl-4-ethyl-4-piperidinol (45) in carbon tetrachloride solution showed an unbonded hydroxyl stretching vibration at 3616 cm<sup>-1</sup> and a bonded hydroxyl stretching vibration at 3400 cm<sup>-1</sup>, in which the ΔV<sub>OH</sub> shift was 216 cm<sup>-1</sup> (see Figure V, Curve E).

NMR Spectrum: (CCl<sub>4</sub>, No. 1549): 7.75 (s,3, -N-CH<sub>3</sub>), 7.98 (s,1, -OH), 8.80 (s,6, -2CH<sub>3</sub>), 8.94 (s,6, -2CH<sub>3</sub>), 8.54-9.14 (m).

1,2,2,6,6-Pentamethyl-4-phenyl-4-piperidinol (19).

The reaction of 1,2,2,6,6-pentamethyl-4-piperidone (70) with phenyl lithium according to the procedure of Lyle<sup>15</sup> gave 1,2,2,6,6-pentamethyl-4-phenyl-4-piperidinol (19). Purification of the picrate by recrystallization from 95% ethanol gave a

yellow powder, m.p. 201-3°. The picrate was dissolved in a minimum amount of sodium hydroxide and extracted with ether. The combined ether layers were dried over potassium carbonate and evaporated to yield 1,2,2,6,6-pentamethyl-4-phenyl-4-piperidinol (19), as a viscous liquid.

Gas Chromatographic Analysis. The base was homogeneous to gas chromatographic analysis having a retention time of 5.3 minutes using a 1 meter Carbowax 20M chromosorb W column at 190° and 15 psi.

Infrared Spectrum: A 0.005 molar solution of 1,2,2,6,6-pentamethyl-4-phenyl-4-piperidinol (19) in carbon tetrachloride solution showed a  $\pi$ -bonded hydroxyl stretching vibration at  $3612\text{ cm}^{-1}$  and a bonded hydroxyl stretching vibration at  $3370\text{ cm}^{-1}$ , in which the  $\Delta V_{\text{OH}}$  shift was  $242\text{ cm}^{-1}$ ; lit.<sup>15</sup>  $3555\text{ cm}^{-1}$  (unbonded) and  $3350\text{ cm}^{-1}$  (bonded) in 0.022 molar solution of 19 in carbon tetrachloride solution (see Figure VI, Curve K).

NMR Spectrum: ( $\text{CCl}_4$ , No. 797): 2.74 (m, 5,  $-\text{C}_6\text{H}_5$ ), 6.98 (s, 1,  $-\text{OH}$ ), 7.74 (s, 3,  $\text{N}-\text{CH}_3$ ), 8.18 (s, 4), 8.73 (s, 6,  $-\text{2CH}_3$ ), 8.90 (s, 6,  $-\text{2CH}_3$ ).

2,2,6,6-Tetramethyl-4-phenyl-4-piperidinol (66). A solution of 13.7 g. (0.087 mole) of bromobenzene in 75 ml. of anhydrous ether was added dropwise to a suspension of 1.2 g. (0.174 mole) of freshly cut lithium ribbon in 50 ml. of anhydrous ether. After stirring at room temperature for 2.5 hrs., a solution of 4.5 g. (0.029 mole) of 2,2,6,6-tetramethyl-4-piperidone (70) dissolved in 50 ml. of anhydrous ether was added dropwise, and the resulting mixture was stirred at room temperature for 6 hrs. The reaction was carried out according to the procedure of Lyle<sup>15</sup> to yield, after recrystallization

from n-heptane, 4.0 g. (60%) of 2,2,6,6-tetramethyl-4-phenyl-4-piperidinol (60) as long white needles, m.p. 127.5-130°; lit.<sup>49</sup>, 131.5°; lit.<sup>50</sup>, 131°.

Anal. Calcd. for  $C_{15}H_{23}NO$ : C, 77.20; H, 9.94; N, 6.00. Found<sup>fm</sup>: C, 77.20; H, 9.85; N, 6.06.

Infrared Spectrum. A 0.005 molar solution of 66 in carbon tetrachloride solution showed a  $\pi$ -bonded hydroxyl stretching vibration at  $3610\text{ cm}^{-1}$ , a bonded hydroxyl stretching vibration at  $3393\text{ cm}^{-1}$  and an N-H vibration at  $3344\text{ cm}^{-1}$ . The  $\Delta V_{OH}$  shift was  $217\text{ cm}^{-1}$  (see Figure VI, Curve L).

NMR Spectrum: ( $CCl_3$ , No. 2258): 2.58 (m, 5,  $C_6H_5$ ), 7.40 (s, 1, OH), 8.23 (s, 4), 8.58 (s, 6,  $-2CH_3$ ), 8.81 (s, 6,  $-2CH_3$ ), (see Figure XII, Curve G for the complete spectrum of 66).

2,2,6,6-Tetramethyl-4-phenyl-4-piperidinol Nitrogen Oxide (48). To a solution of 20 ml. of 30% hydrogen peroxide dissolved in 50 ml. of acetone was added dropwise a solution of 2.0 g. (0.0086 mole) of 2,2,6,6-tetramethyl-4-phenyl-4-piperidinol (66) dissolved in 20 ml. of acetone. A trace of ammonium molybdate was added as catalyst. After stirring at room temperature for 8 hrs., the solution was concentrated by evaporation and distilled water was added to the residue. The precipitate which resulted was removed by filtration and washed with distilled water. Recrystallization of the yellow solid with n-heptane gave 0.6 g. (20%) of 2,2,6,6-tetramethyl-4-phenyl-4-piperidinol nitrogen oxide (48) as yellow, feather-like needles, m.p. 122-4°C.

Anal. Calcd. for  $C_{15}H_{22}NO_2$ : C, 72.55; H, 8.93; N, 5.64. Found<sup>fm</sup>: C, 72.98; H, 9.37; N, 5.59.

Infrared Spectrum: A 0.005 molar solution of 48 in carbon tetrachloride solution showed a single  $\pi$ -bonded hydroxyl stretching vibration at  $3606\text{ cm}^{-1}$ .

NMR Spectrum: There were no resonance signals obtained except for a weak aromatic signal at 2.87.

Magnetic Susceptibility. The magnetic susceptibility of 2,2,6,6-tetramethyl-4-phenyl-4-piperidinol nitrogen oxide (48) was 0.91 Bohr Magnetrons, indicative of a paramagnetic molecule.

1-Methyl-2,6-diphenyl-4-piperidone<sup>51</sup> (71). Methylamine was bubbled into a suspension of 20 g. (0.086 mole) of dibenzalacetone<sup>52</sup>, m.p.  $114-115^\circ$ , in 200 ml. of methanol until solution was effected. Approximately 8 to 10 g. of methylamine was dissolved. The solution was allowed to stand at room temperature for 48 hrs. The solvent was removed, and the residual brown oil was dissolved in 100 ml. of ether. An equal amount of water was added to the ethereal solution and on standing at room temperature, the product precipitated at the interface. The product was removed by filtration with suction and was recrystallized from 95% ethanol yielding 16 g. (70.2%) of 1-methyl-2,6-diphenyl-4-piperidone (71), m. p.  $149-151^\circ$ ; lit.<sup>53</sup>, m.p.  $152-3^\circ\text{C}$ .

1-Methyl-2,6-diphenyl-4-piperidinol (39). To a slurry of 1.6 g. (0.04 mole) of lithium aluminum hydride in 50 ml. of ether was added 5.3 g. (0.020 mole) of 1-methyl-2,6-diphenyl-4-piperidone (71) dissolved in 75 ml. of ether. The reaction mixture was heated under reflux for 3 hrs., and worked up according to the procedure for the preparation of 1,3,5-trimethyl-2,6-diphenyl-4-piperidinol (49a), to yield 4.9 g. (91%) of a white solid. Recrystallization of the white solid from

n-heptane gave 1-methyl-2,6-diphenyl-4- $\alpha$ -piperidinol (39) m.p. 165-7°, (lit.<sup>54</sup>, m.p. 164.5-167°) as a cotton-like solid.

Infrared Spectrum: A 0.005 molar solution of 39 in carbon tetrachloride solution showed an unbonded hydroxyl stretching vibration at 3628 cm<sup>-1</sup> (lit.<sup>52</sup>  $\nu_{\text{CCl}_4}$  3618 cm<sup>-1</sup>).

NMR Spectrum: (DCCl<sub>3</sub>, No. 609): 2.78 (m, 10, -C<sub>6</sub>H<sub>5</sub>), 6.92 (d, 2, -CH-Ph), 8.08 (m), 8.30 (s, 3, N-CH<sub>3</sub>).

1,4-Dimethyl-2,6-diphenyl-4-piperidinol (41). Methyl bromide gas was bubbled into 50 ml. of anhydrous ether until 8.3 g. (0.093 moles) were absorbed. This solution was added dropwise to a suspension of 2.2 g. (0.093 moles) of magnesium turnings in 50 ml. of anhydrous ether. After all the magnesium turnings had undergone reaction, an ether suspension of 7.0 g. (0.026 mole) of 1-methyl-2,6-diphenyl-4-piperidone (71) in 250 ml. of ether was added. Stirring was maintained at reflux temperature for 8 hours. The reaction was worked up according to the procedure for the preparation of 1,2,2,4,6,6-hexamethyl-4-piperidinol (44) to yield 5.3 g. of a white solid, m.p. 146-8°. Recrystallization of the white solid from n-heptane gave 4.8 g. (65%) of 1,4-dimethyl-2,6-diphenyl-4-piperidinol as white crystals, m.p. 151.5-153°; lit.<sup>50</sup>, m.p. 147-8°.

Anal. Calcd. for C<sub>19</sub>H<sub>23</sub>NO: C, 81.10; H, 8.24.  
Found<sup>ws</sup>: C, 81.15; H, 8.28.

Infrared Spectrum: A 0.0025 molar solution of 41 in carbon tetrachloride solution showed an unbonded hydroxyl stretching vibration at 3621 cm<sup>-1</sup>.

NMR Spectrum: (CCl<sub>4</sub>, No. 4157): 2.70 (m, 10, C<sub>6</sub>H<sub>5</sub>), 6.48 (t, 2, CH-Ph), 8.18 (s, 3, N-CH<sub>3</sub>), 8.33 (m, 4), 8.79 (s, 3, -CH<sub>3</sub>), (see Figure XII, Curve H for the complete spectrum of 41).

trans-2-Phenylcyclohexanol (34). trans-2-Phenylcyclohexanol (34) was obtained by fractional crystallization of a commercial sample of 2-phenylcyclohexanol in a dry ice acetone bath. The trans isomer was obtained as white needles, m.p. 52-6° (lit.<sup>55,56</sup>, m.p. 57-8°; 56-7°).

Gas Chromatographic Analysis. The trans isomer was homogeneous to gas chromatographic analysis having a retention time of 11.6 minutes using a 2 meter Carbowax 20M on chromosorb W column at 160° and 10 psi. It was compared to the commercial mixture which gave two peaks, under similar conditions, 11.6 minutes, 56.4% trans, and 9.0 minutes, 43.6% cis isomer.

Infrared Spectrum: A 0.005 molar solution of 34 in carbon tetrachloride solution showed a  $\pi$ -bonded hydroxyl stretching vibration at  $3607\text{ cm}^{-1}$  and a shoulder at  $3628\text{ cm}^{-1}$  (unbonded), in which the  $\Delta\nu_{\text{OH}}$  shift was  $21\text{ cm}^{-1}$  (lit.<sup>57</sup>,  $3621\text{ cm}^{-1}$  (sh) and  $3598\text{ cm}^{-1}$ ).

NMR Spectrum: ( $\text{DCCl}_3$ , No. 1784): 2.80 (s,5,  $\text{C}_6\text{H}_5$ ), 6.56 (m,1,  $\text{CH-OH}$ ), 8.03 (s,1,  $\text{OH}$ ), 8.50 (m,8), (see Figure IV, Curve B for the carbinol proton of 34).

3,5-Dimethyl-2,6-diphenyl-4-piperidone (67). 3,5-Dimethyl-2,6-diphenyl-4-piperidone (67) was prepared according to the procedure of Noller and Baliah.<sup>58</sup> A solution of 12.2 g. (0.2 mole) of anhydrous ammonium acetate in 20 ml. of glacial acetic acid was added to a solution of 41.6 g. (0.4 mole) of benzaldehyde and 17.2 g. (0.2 mole) of 3-pentanone. The reaction mixture was heated under reflux for 3 hrs., and on neutralization a precipitate formed. The precipitate was removed by filtration, and washed with distilled water to give 26 g. (48%) of 3,5-dimethyl-2,6-diphenyl-4-piperidone (67), m.p., 140-2°. Recrystallization of the solid from 95% ethanol

gave 22 g. (40%) of 67 as long white needles, m.p. 132-5° (lit.<sup>58</sup>, 132-3°).

NMR Spectrum: ( $\text{CCl}_4$ , No. 1635): 2.72 (m, 10,  $\text{C}_6\text{H}_5$ ), 6.51 (d, 2,  $\underline{J} = 10$  Hz,  $\text{CH-Ph}$ ), 7.40 (m, 2, band width = 30.5 Hz), 8.08 (s, 1, N- $\underline{\text{H}}$ ), 9.28 (d, 6,  $\underline{J} = 7$  Hz,  $-2\text{CH}_3$ ).

1,3,5-Trimethyl-2,6-diphenyl-4-piperidone (68). A mixture of 22 g. (0.079 mole) of 3,5-dimethyl-2,6-diphenyl-4-piperidone (57) and 22 g. of anhydrous potassium carbonate was added to a solution of 11 g. (0.078 mole) of methyl iodide dissolved in 100 ml. of acetone. The reaction mixture was heated under reflux for 4 hrs. The acetone was evaporated from the reaction mixture and 50 ml. of distilled water and ammonium hydroxide were added. The solid which formed on neutralization was removed by filtration, washed with distilled water, and recrystallized from 95% ethanol to give 18.5 g. (80%) of 68 as white needles, m.p. 86-88° (lit.<sup>58</sup>, m.p. 91-2°). The hydrochloride was prepared by the usual method to give a white solid, m.p. 234-6°.

NMR Spectrum: Base ( $\text{CCl}_4$ , No. 1590): 2.67 (m, 10,  $\text{C}_6\text{H}_5$ ), 7.06 (m, 4), 8.33 (s, 3, N- $\text{CH}_3$ ), 9.27 (d, 6,  $\underline{J} = 6$  Hz,  $2\text{CH}_3$ ), (see Figure XII, Curve K for complete spectrum of 68).

3,5-Dimethyl-2,6-diphenyl-4-piperidinol (40). To a slurry of 2.05 g. (0.054 mole) of lithium aluminum hydride in 50 ml. of dry tetrahydrofuran (THF) contained in a 250 ml. one-neck flask with a U-tube extension was added 5.0 g. (0.018 mole) of 3,5-dimethyl-2,6-diphenyl-4-piperidone (67) dissolved in 100 ml. of dry THF. The reaction mixture was stirred and heated under reflux for 7 hrs. After allowing the reaction mixture to cool, the excess lithium aluminum hydride was decomposed with dilute sodium hydroxide. The tetrahydrofuran solution was decanted from the precipitate, which was



washed with two 25 ml. portions of dry THF. The combined tetrahydrofuran solutions were evaporated in the hood overnight to yield 4.4 g. (87%) of a white solid, m.p., 119-123°. Analysis of the nmr spectrum indicated a mixture of two isomers; 71%  $\alpha$  isomer and 29%  $\beta$  isomer. The white solid was chromatographed over a column of 75 g. of neutral alumina using light petroleum ether (b.p. 40-60°); (1:1) light petroleum ether-benzene; benzene; (1:1) benzene-ether; and ether as eluents. The reduction product was dissolved in a minimum amount of benzene and added to the column. Two 40 ml. fractions were collected with each eluent and the eluent evaporated in the hood overnight. The benzene fractions gave white crystals, m.p. 106-108°, whose nmr spectrum indicated 100%  $\beta$  form (lit.<sup>38</sup>, m.p. 111-2°). On the other hand, the ether fractions gave a white solid, m.p., 121-5°, whose nmr spectrum indicated 89%  $\alpha$  form (lit.<sup>38</sup>, m.p. 133-4°).

Infrared Spectrum:  $\beta$ -3,5-Dimethyl-2,6-diphenyl-4-piperidinol (40b) - The hydroxyl stretching vibration in the infrared spectrum determined as a 0.005 molar solution in carbon tetrachloride gave a symmetrical singlet at  $3654\text{ cm}^{-1}$  and a peak at  $3332\text{ cm}^{-1}$  due to the N-H stretching absorption of the amine (see Figure VI, Curve A). A 0.00195 molar solution of  $\alpha$ -3,5-dimethyl-2,6-diphenyl-4-piperidinol (40a) in carbon tetrachloride showed a doublet in the hydroxyl stretching region at  $3652\text{ cm}^{-1}$  and  $3614\text{ cm}^{-1}$ , and a peak at  $3334\text{ cm}^{-1}$  due to N-H stretching of the amine (see Figure V, Curve H).

3,5-Dimethyl-2,4,6-triphenyl-4-piperidinol (61). A solution of 10.3 g. (0.066 mole) of bromobenzene in 50 ml. of anhydrous ether was added dropwise to a suspension of 0.92 g. (0.132 mole) of freshly cut lithium ribbon in 50 ml. of anhydrous ether. After 3 hrs., a solution of 2.0 g. (0.007

mole) of 3,5-dimethyl-2,6-diphenyl-4-piperidone (67) in ether was added dropwise and the reaction was allowed to stir for 4 hrs. at room temperature. The reaction was worked up according to the procedure of Lyle<sup>15</sup> to yield 1.5 g. (59%) of 3,5-dimethyl-2,4,6-triphenyl-4-piperidinol (61) as pale yellow crystals, m.p. 147-151° after recrystallization from n-heptane.

Anal. Calcd. for  $C_{25}H_{27}NO$ : C, 83.99; H, 7.61; N, 3.92.  
Found<sup>ws</sup>: C, 84.09; H, 7.47; N, 3.98.

Infrared Spectrum: A 0.005 molar solution of 61 in carbon tetrachloride solution showed a hydroxyl stretching vibration at  $3624\text{ cm}^{-1}$  and a peak at  $3332\text{ cm}^{-1}$  due to N-H stretching of the amine.

NMR Spectrum: ( $CCl_4$ , No. 1630): 2.33 (m, 15,  $3C_6H_5$ ), 5.67 (d, 2,  $J = 10\text{ Hz}$ ,  $\underline{CH}$ -Ph), 7.41 (m, 2, band width =  $31.5\text{ Hz}$ ), 8.00 (s, 1, OH), 9.27 (d, 6,  $J = 7\text{ Hz}$ ,  $2\underline{CH}_3$ ).

1,3,5-Trimethyl-2,6-diphenyl-4-piperidinol (49). To a slurry of 1.94 g. (0.051 mole) of lithium aluminum hydride in 50 ml. of anhydrous ether contained in a 250 ml. one-neck flask was added 5.0 g. (0.017 mole) of 1,3,5-trimethyl-2,6-diphenyl-4-piperidone (68) dissolved in 100 ml. of dry ether. The reaction mixture was heated under reflux for 5 hrs. and after cooling, the excess lithium aluminum hydride was decomposed with dilute sodium hydroxide. The precipitate which formed was removed by filtration, was cooled, and was washed carefully with three 25 ml. portions of ether. The combined ether solutions were dried over anhydrous potassium carbonate and evaporated to give 4.2 g. of a white solid. Recrystallization of the white solid from n-heptane gave 4.0 g. (79.8%) of a mixture of 52% axial (49b) and 48% equatorial (49a) isomers of 1,3,5-trimethyl-2,6-diphenyl-4-piperidinol (49),

m.p. 123-7°. This mixture was chromatographed over a column of 45 g. of Florisil using petroleum ether (40-60°); petroleum ether-benzene (1:1); benzene; benzene-ether (1:1); and ether as eluents. Fractions were collected every 30 ml. and evaporated. The petroleum ether-benzene (1:1) fractions gave a white solid, m.p. 94-7°. An analysis of the benzylic protons in the nmr spectrum indicated that this mixture consisted of 91%  $\beta$  form (49); lit.<sup>38</sup>, m.p. 98-9°. On the other hand the benzene-ether (1:1) and ether fractions yielded a white solid, m.p. 127-131°, whose nmr spectrum indicated 90%  $\alpha$  isomer (49a); lit.<sup>38</sup>, m.p. 134-5°.

Infrared Spectrum: A 0.005 molar solution of  $\beta$ -1,3,5-trimethyl-2,6-diphenyl-4-piperidinol (49b) in carbon tetrachloride solution showed an unbonded hydroxyl stretching vibration at  $3650\text{ cm}^{-1}$  (see Figure VI, Curve C). A 0.005 molar solution of  $\alpha$ -1,3,5-trimethyl-2,6-diphenyl-4-piperidinol (49a) in carbon tetrachloride solution showed two hydroxyl stretching vibrations, one at  $3652\text{ cm}^{-1}$  and the other at  $3615\text{ cm}^{-1}$  (see Figure VI, Curve B).

1,3,5-Trimethyl-2,4,6-triphenyl-4-piperidinol (60).

A solution of 8.05 g. (0.051 mole) of bromobenzene in 50 ml. of ether was added dropwise to a suspension of 0.72 g. (0.102 mole) of freshly cut lithium ribbon in 50 ml. of ether. After all the lithium had undergone reaction, a solution of 5.0 g. (0.017 mole) of 1,3,5-trimethyl-2,6-diphenyl-4-piperidone (68) in ether was added over the period of 0.5 hr. Stirring was maintained at room temperature for 4.5 hrs. The unreacted phenyllithium was hydrolyzed with water, and the organic material was salted out with potassium carbonate. The water layer was drawn off and extracted three times with 50 ml. portions of ether. The combined organic layers were dried

over potassium carbonate and evaporated to give 4.5 g. (71%) of a white solid. Recrystallization of the white solid from n-heptane gave 1,3,5-trimethyl-2,4,6-triphenylpiperidin-4-ol (60) as white needles, m.p. 249-252°.

Anal. Calc. for  $C_{26}H_{29}NO$ : C, 84.05; H, 7.87; N, 3.77.  
Found<sup>WS</sup>: C, 83.91; H, 7.72; N, 3.62.

Infrared Spectrum: A 0.005 molar solution of 60 in carbon tetrachloride solution showed only a  $\pi$ -bonded hydroxyl stretching vibration at  $3621\text{ cm}^{-1}$ .

NMR Spectrum: ( $CCl_4$ , No. 1636): 2.40 (m, 15,  $3C_6H_5$ ), 6.39 (d, 2,  $J = 10.5\text{ Hz}$ ,  $CH-Ph$ ), 7.32 (m, 2), 7.98 (s, 3,  $N-\underline{CH_3}$ ), 9.39 (d, 6,  $J = 7\text{ Hz}$ ,  $2\underline{CH_3}$ ).

2,6-Dimethyl-cyclohexanol (52) - Lithium Aluminum

Hydride Reduction. To a slurry of 5.5 g. (0.145 mole) of lithium aluminum hydride in 100 ml. of anhydrous ether contained in a 250 ml. one-neck, round bottom flask was added 10.0 g. (0.079 mole) of 2,6-dimethylcyclohexanone<sup>42</sup> dissolved in 50 ml. of anhydrous ether. The reaction mixture was heated under reflux for 4 hrs., and worked up according to the procedure for the preparation of 1,3,5-trimethyl-2,6-diphenyl-4-piperidinol (49) to yield 5.4 g. of a mixture of three isomers of 2,6-dimethylcyclohexanol (52), b.p. 160-168° at atmospheric pressure.

Gas Chromatographic Analysis. Using a 4-foot column of 20% silicone (GE-XE60) nitrile gum on chromosorb W-KOH wash at 85° and a flow rate of 75 ml./min., the alcohol mixture consisted of 35% cis-2-cis-6-dimethylcyclohexanol (52b), 11.5 min. retention time; 47% trans-2-trans-6-dimethylcyclohexanol (52a), 13.3 min. retention time; and 18% cis-2-trans-6-dimethylcyclohexanol (52c), 16.4 min. retention time. These data are the average of two determinations estimated by peak area,

using a planimeter and by peak height.

NMR Spectrum: ( $\text{DCCl}_3$ ) An analysis of the carbinol protons showed the alcohol mixture to consist of 39% cis-2-cis-6-dimethylcyclohexanol (52b), 209 Hz downfield from TMS, lit.<sup>59</sup>; 208 Hz; 45% trans-2-trans-6-dimethylcyclohexanol (52a), 146 Hz downfield from TMS, lit.<sup>59</sup>, 145 Hz; and 16% cis-2-trans-6-dimethylcyclohexanol (52c), 198 Hz downfield from TMS, lit.<sup>59</sup>, 193 Hz. These data are the average of two determinations using the area of the carbinol protons determined by a K & E planimeter.

2,6-Dimethylcyclohexanol (52) - Lithium Aluminum Tri-tert-butoxyhydride Reduction. To a slurry of 12 g. (0.047 mole) lithium aluminum tri-t.-butoxyhydride in 50 ml. one-neck, round bottom flask was added dropwise 5.0 g. (0.40 mole) of 2,6-dimethylcyclohexanone<sup>42</sup> dissolved in 50 ml. of dry tetrahydrofuran. The reaction mixture was exothermic on addition of the ketone. The mixture was stirred at room temperature for 7 hrs. and worked up according to the procedure for the preparation of 3,5-dimethyl-2,6-diphenyl-4-piperidinol (40) to yield 2.9 g. of a colorless liquid, b.p. 160-168° at atmospheric pressure, after distillation.

Gas Chromatographic Analysis. Using a 4-foot column of 20% silicone (GE-XE60) nitrile gum on chromosorb W-KOH wash at 85° and a flow rate of 75 ml./min., the alcohol mixture was shown to consist of 50% cis-2-cis-6-dimethylcyclohexanol (52b), 11.5 min. retention time; 34% trans-2-trans-6-dimethylcyclohexanol (52a), 13.2 min. retention time; and 16% cis-2-trans-6-dimethylcyclohexanol (52c), 16.5 min. retention time. These data are the average of two determinations using a planimeter to determine the area and the peak height method (see Figure IX, Curve B).

NMR Spectrum: ( $\text{DCCl}_3$ ) An analysis of the carbinol protons showed the alcohol mixture to consist of 50% cis-2-cis-6-dimethylcyclohexanol (52b), 204 Hz downfield from TMS, lit.<sup>59</sup>, 208 Hz; 32% trans-2-trans-6-dimethylcyclohexanol (52a), 150 Hz downfield from TMS, lit.<sup>59</sup>, 145 Hz; and 18% cis-2-trans-6-dimethylcyclohexanol (52c), 181 Hz downfield from TMS, lit.<sup>59</sup>, 193 Hz. These data are the average of two determinations based on the area of the signal of carbinol protons determined by a K & E planimeter (see Figure XI, Curve C).

trans-2-trans-6-Dimethylcyclohexanol (52a). trans-2-trans-6-Dimethylcyclohexanol (52a) was collected on the Aerograph Autoprep Model A-700 from the mixture of the three isomers of dimethylcyclohexanol (52) as white needles, m.p. 49.5-52° (lit.<sup>60</sup>, m.p. 52.5°).

Infrared Spectrum: A 0.005 molar solution of trans-2-trans-6-dimethylcyclohexanol (52a) in carbon tetrachloride showed a doublet in the hydroxyl stretching region at 3652  $\text{cm}^{-1}$  and 3614  $\text{cm}^{-1}$  (see Figure VI, Curve D).

## SUMMARY

The conformational equilibrium of 3-piperidinols was studied by infrared and nuclear magnetic resonance spectroscopy, which showed that intramolecular hydrogen bonding of the hydroxyl group with nitrogen decreased the apparent steric requirements of the axial hydroxyl. The strength of the hydrogen bond was estimated. The composition of the equilibrium was estimated by the averaged coupling constants in the NMR, and by the intensity of the unbonded hydroxyl absorption in the infrared.

A study of the variation in concentration, solvent and temperature was completed using NMR spectroscopy to determine the effect on the composition of the conformational equilibrium of 3-piperidinols. It was found that intramolecular hydrogen bonding at higher concentrations, and in certain solvents, gave evidence of a decrease in the axial conformation in the equilibrium mixture, and an increase in the free energy difference.

In estimating the composition of the equilibrium of piperidinols by the intensity of the unbonded hydroxyl absorption in the infrared, it was found that it was not necessary to use only secondary and tertiary piperidinols as models, but any normal secondary or tertiary alcohol was sufficient. The integrated intensities of the unbonded hydroxyl absorption bands in the infrared spectra of the model compounds provided a method to estimate the conformational equilibrium of 3-piperidinols and 1,2,2,6,6-pentamethyl-4-piperidinols.

The evaluation of several approaches to the conformational analysis of the cis and trans isomers of 1-methyl-4-phenyl-3-piperidinol was given. The conformational equilibria

of not only 3- and 4-piperidinols can be estimated by infrared spectroscopy, but this approach can be extended to the estimation of the composition of the conformational equilibria of a variety of systems.

A conformational study of the alpha isomers of the 3,5-dimethyl-2,6-diphenyl-4-piperidinols by infrared spectroscopy indicated that the anomalous spectra resulted from steric interference with the hydroxyl stretching vibration rather than from intramolecular hydrogen bonding. Thus, the spectral data can be explained on the basis of a slightly distorted chair conformer and there is no evidence which requires the postulation of boat conformations as was previously reported in the literature.



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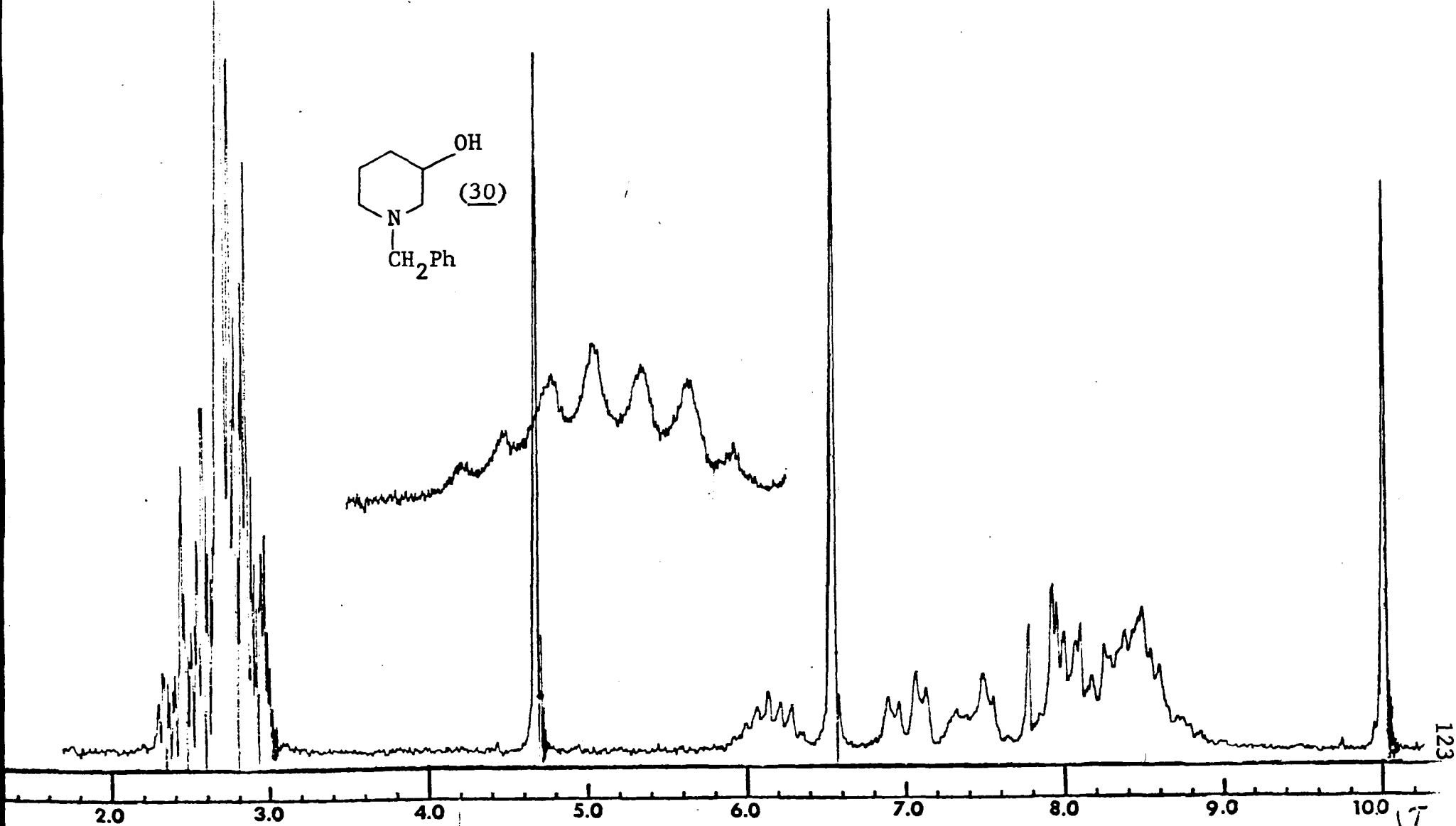
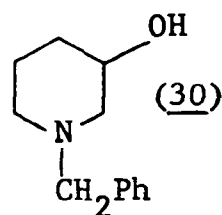
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## APPENDIX

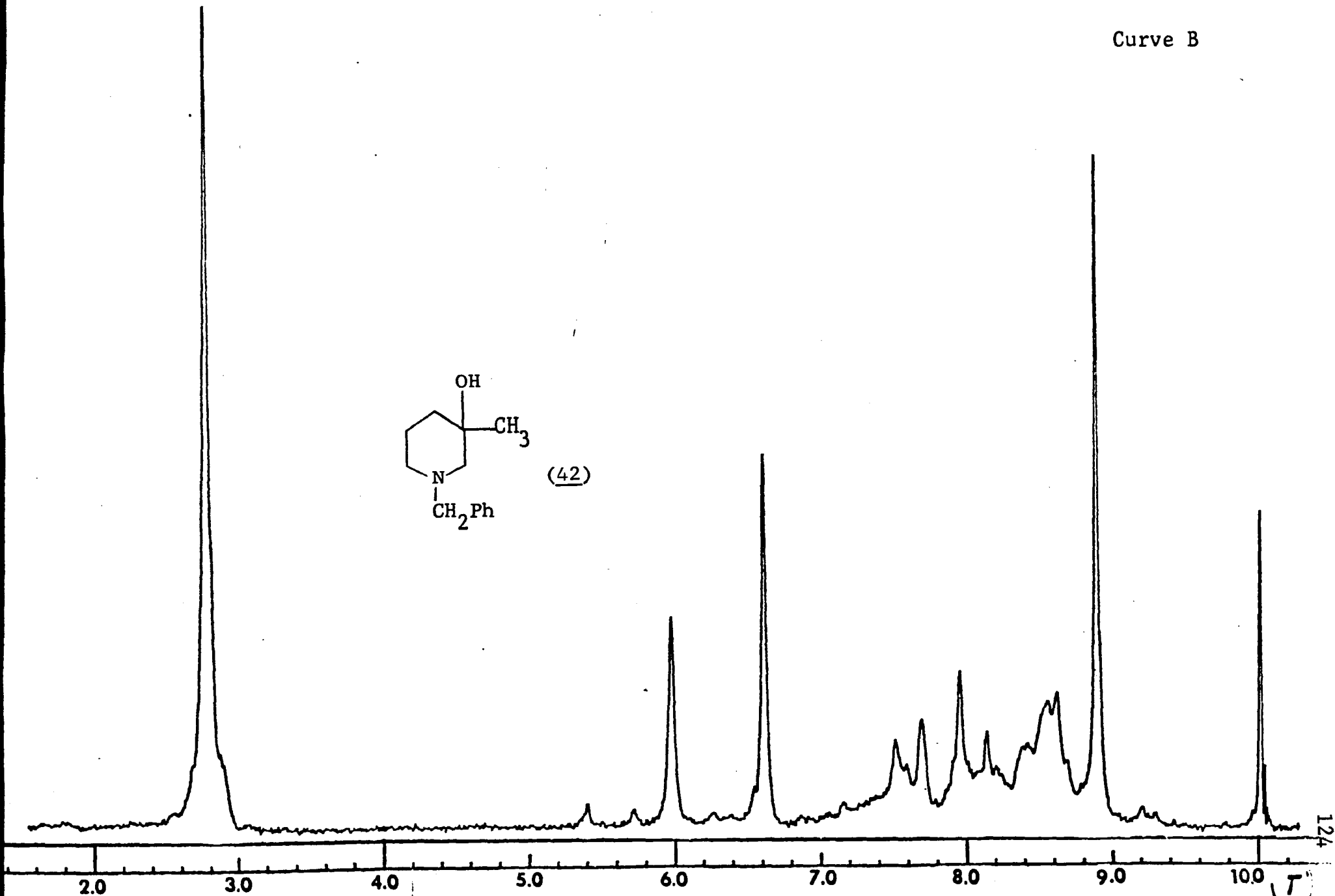
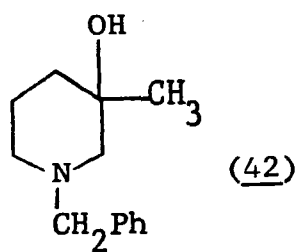
Figure XII

Curve A

1000 Hz NMR Spectra of Various Piperidine Derivatives

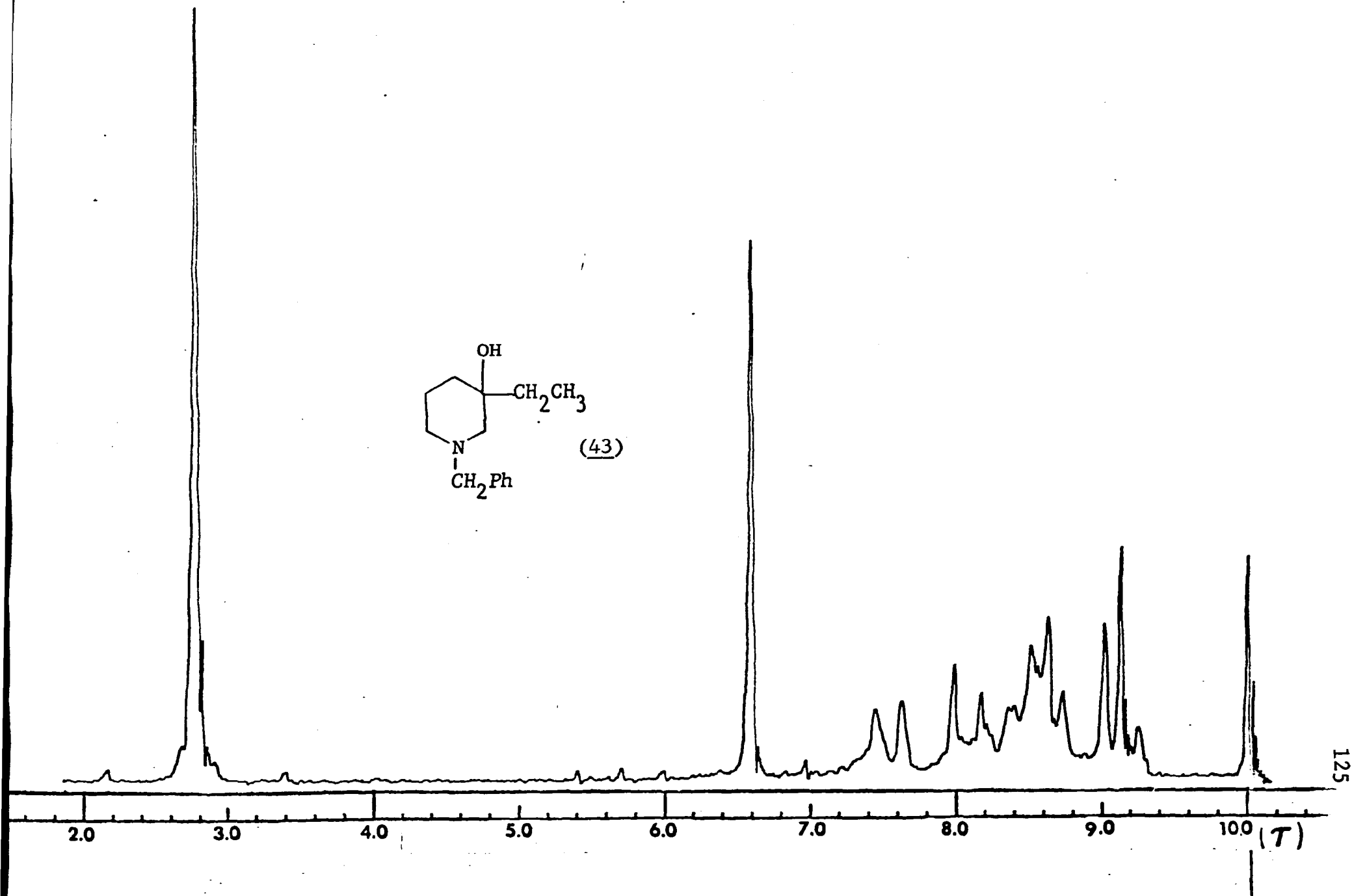
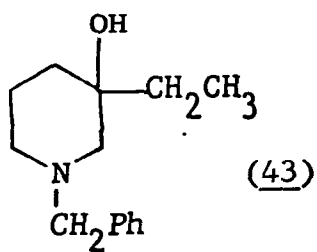


Curve B

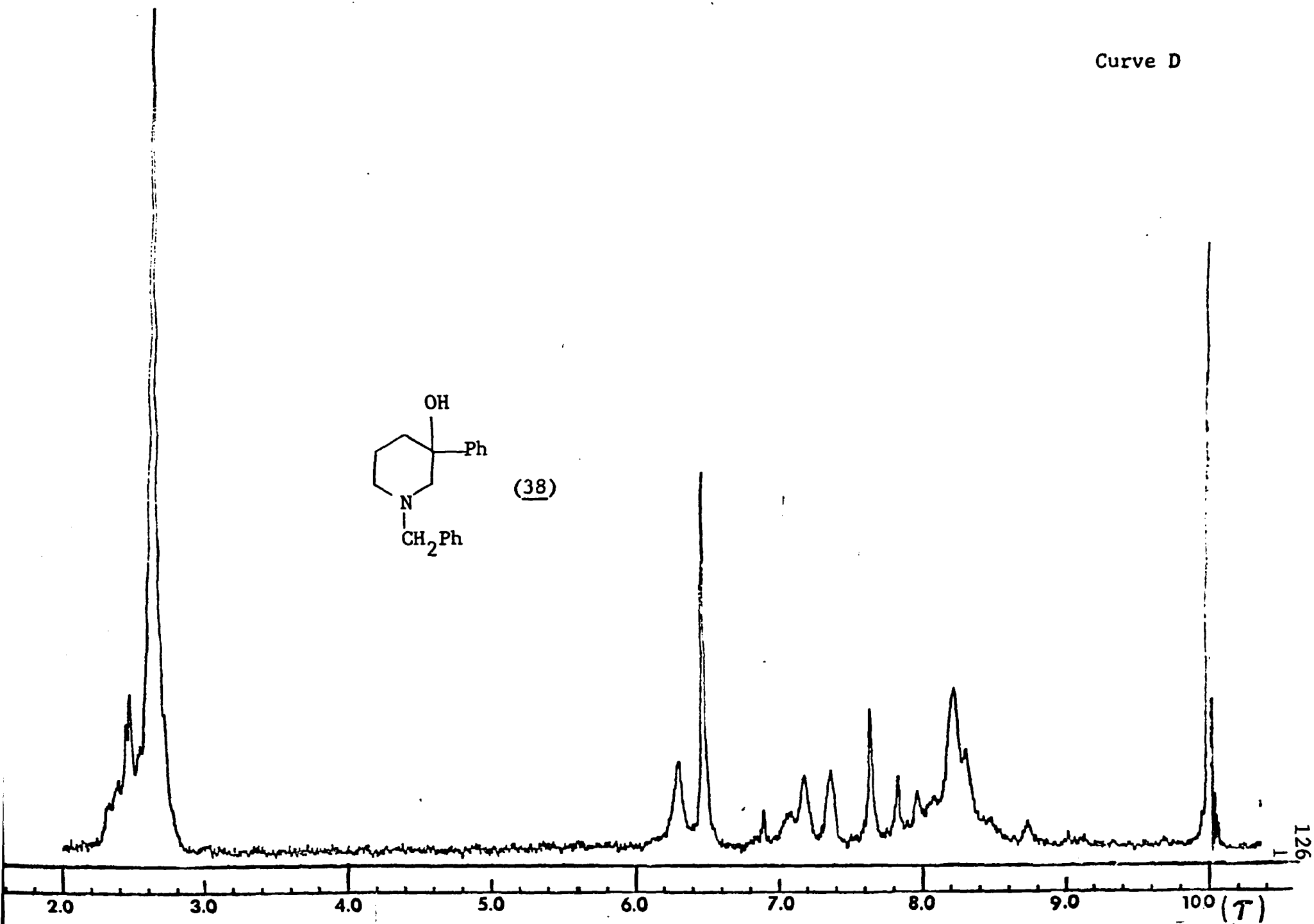
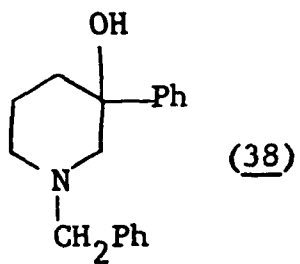




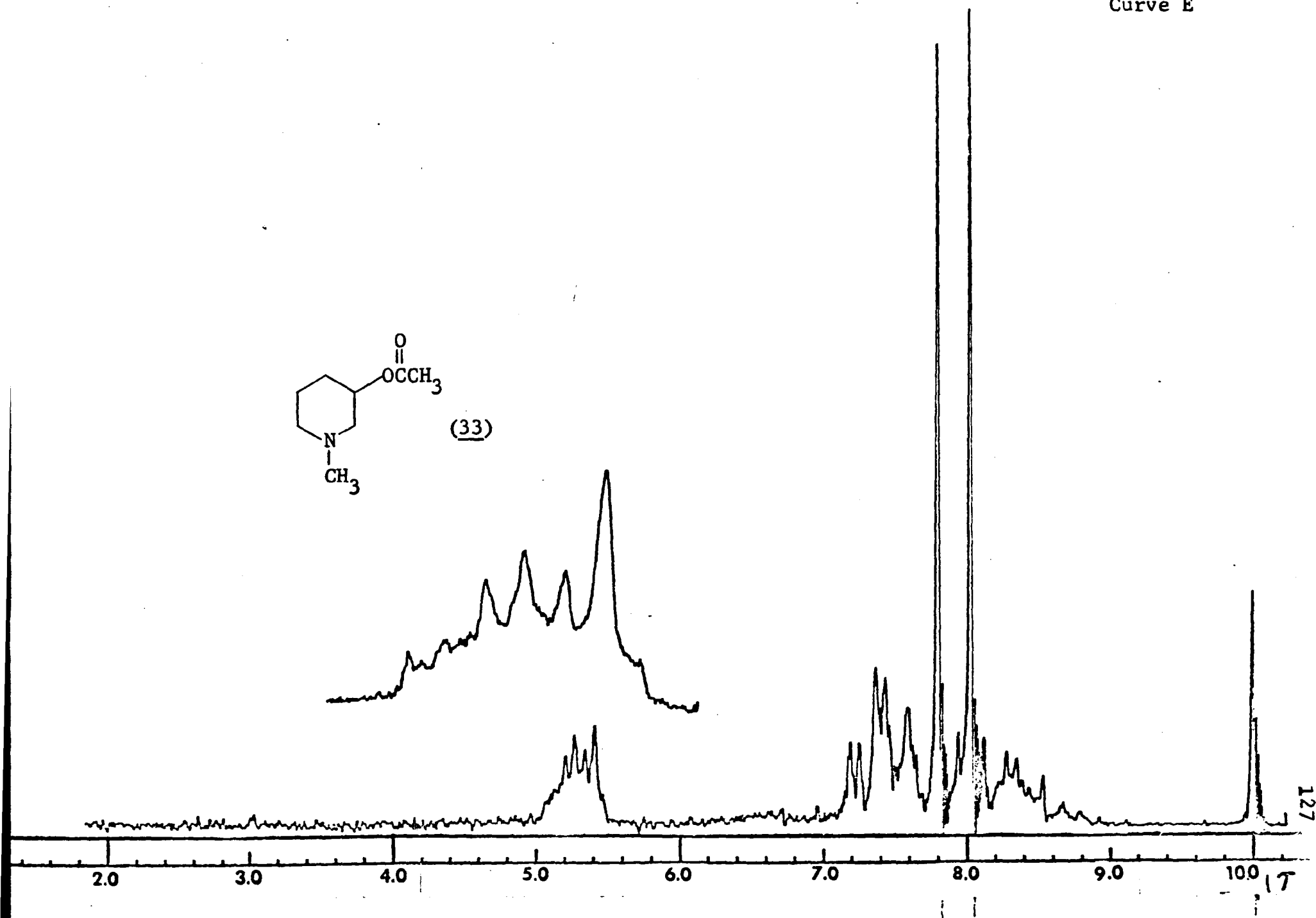
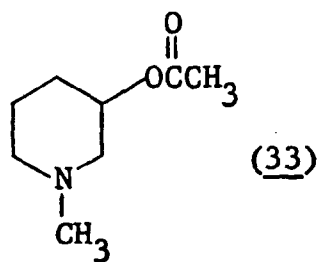
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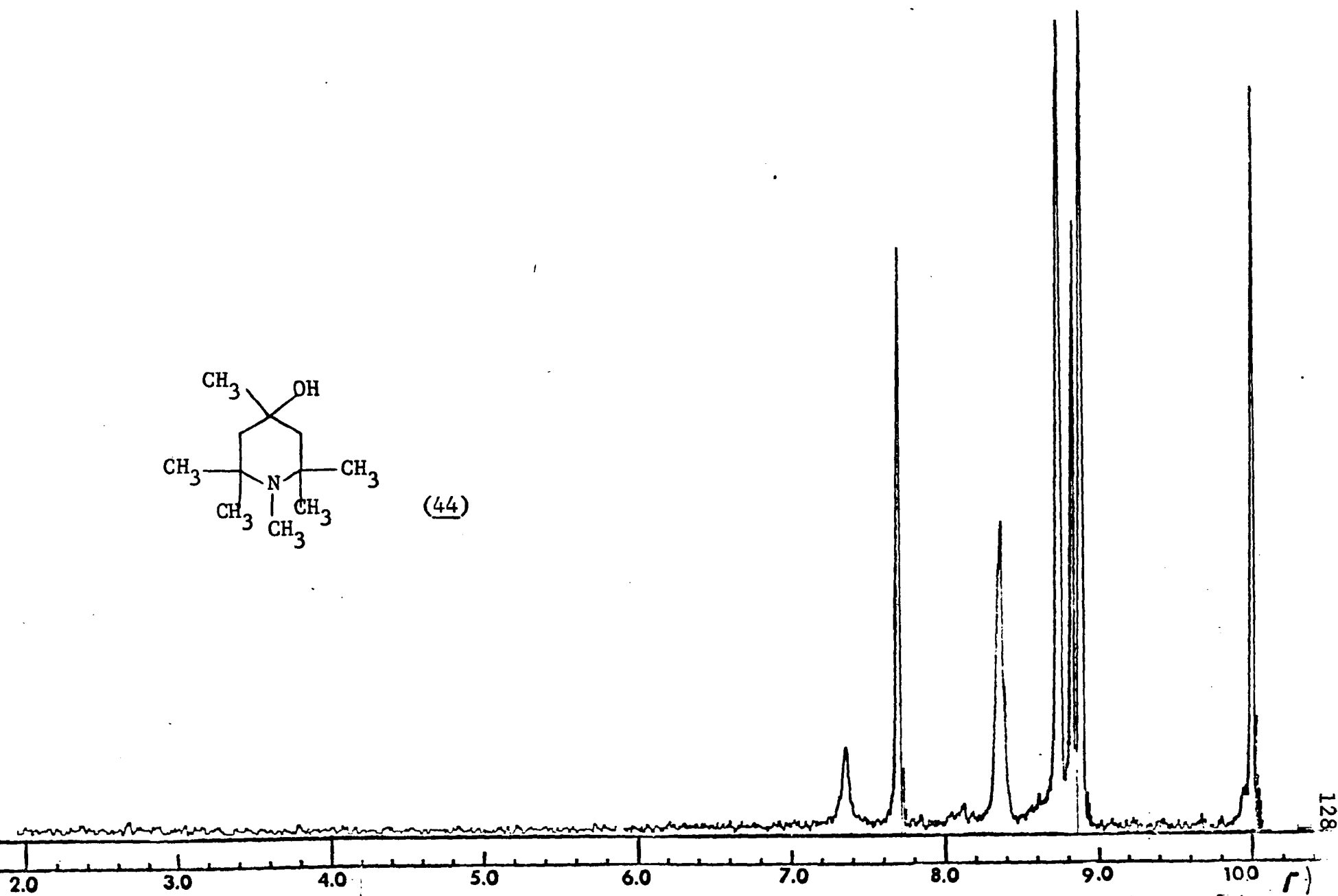
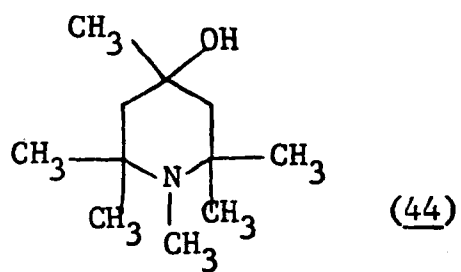
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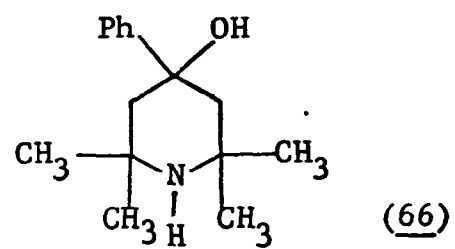


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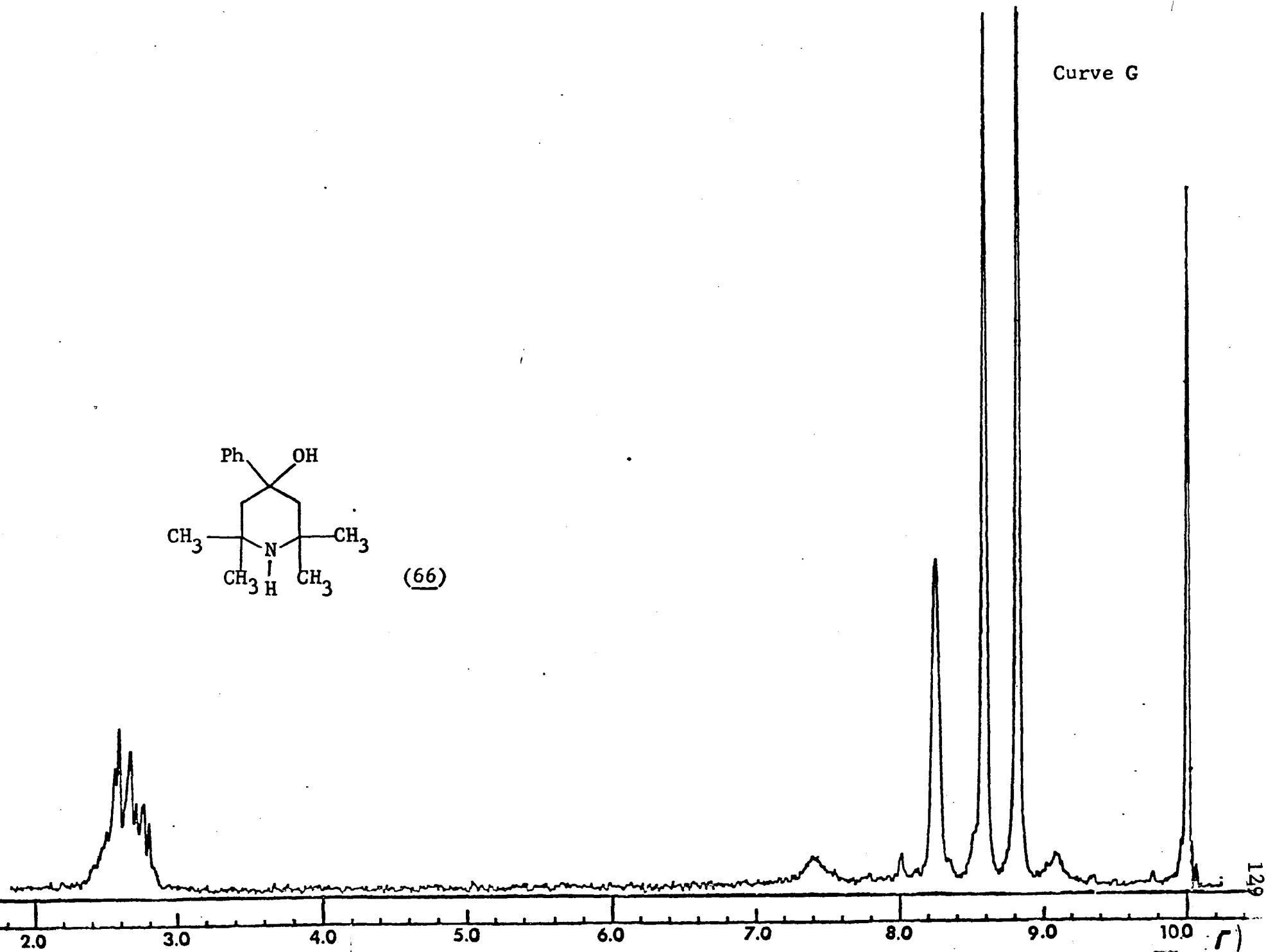


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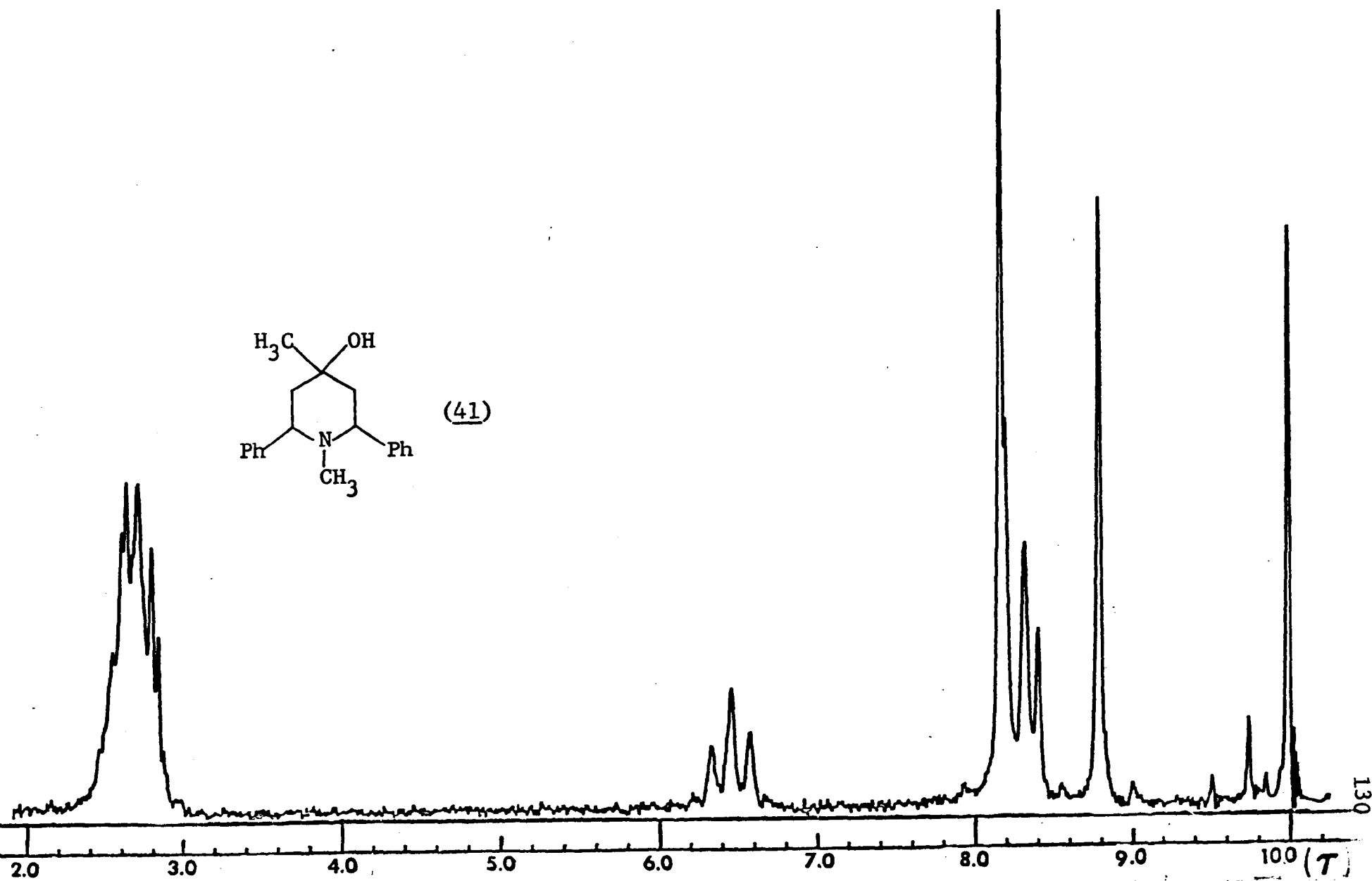
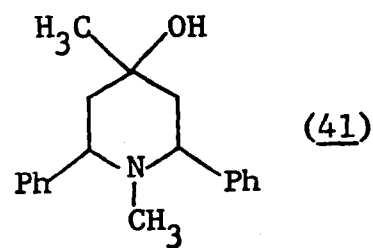




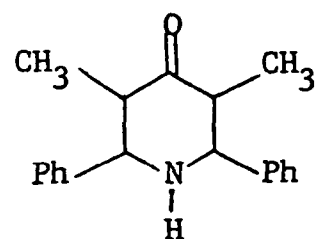
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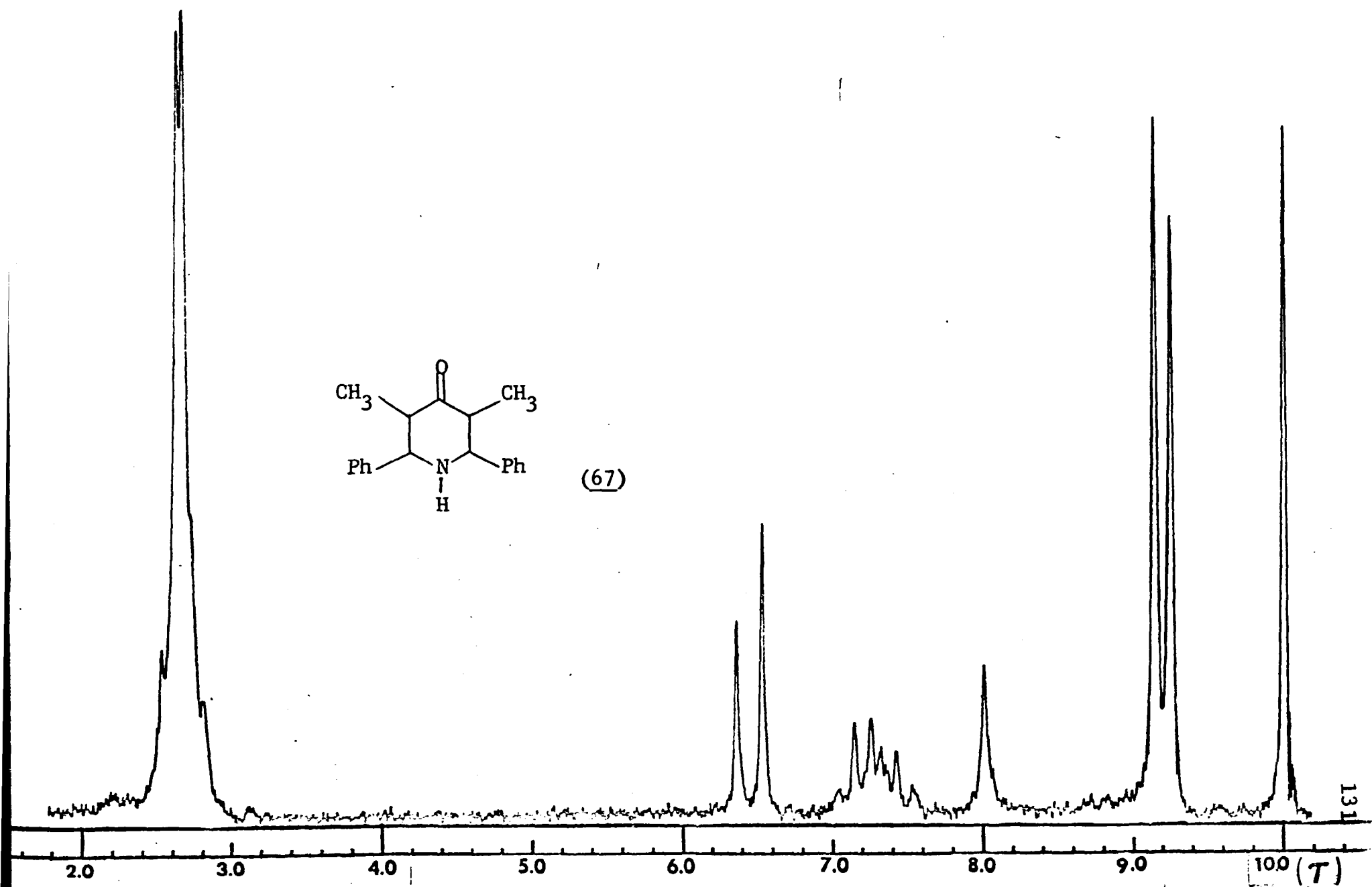
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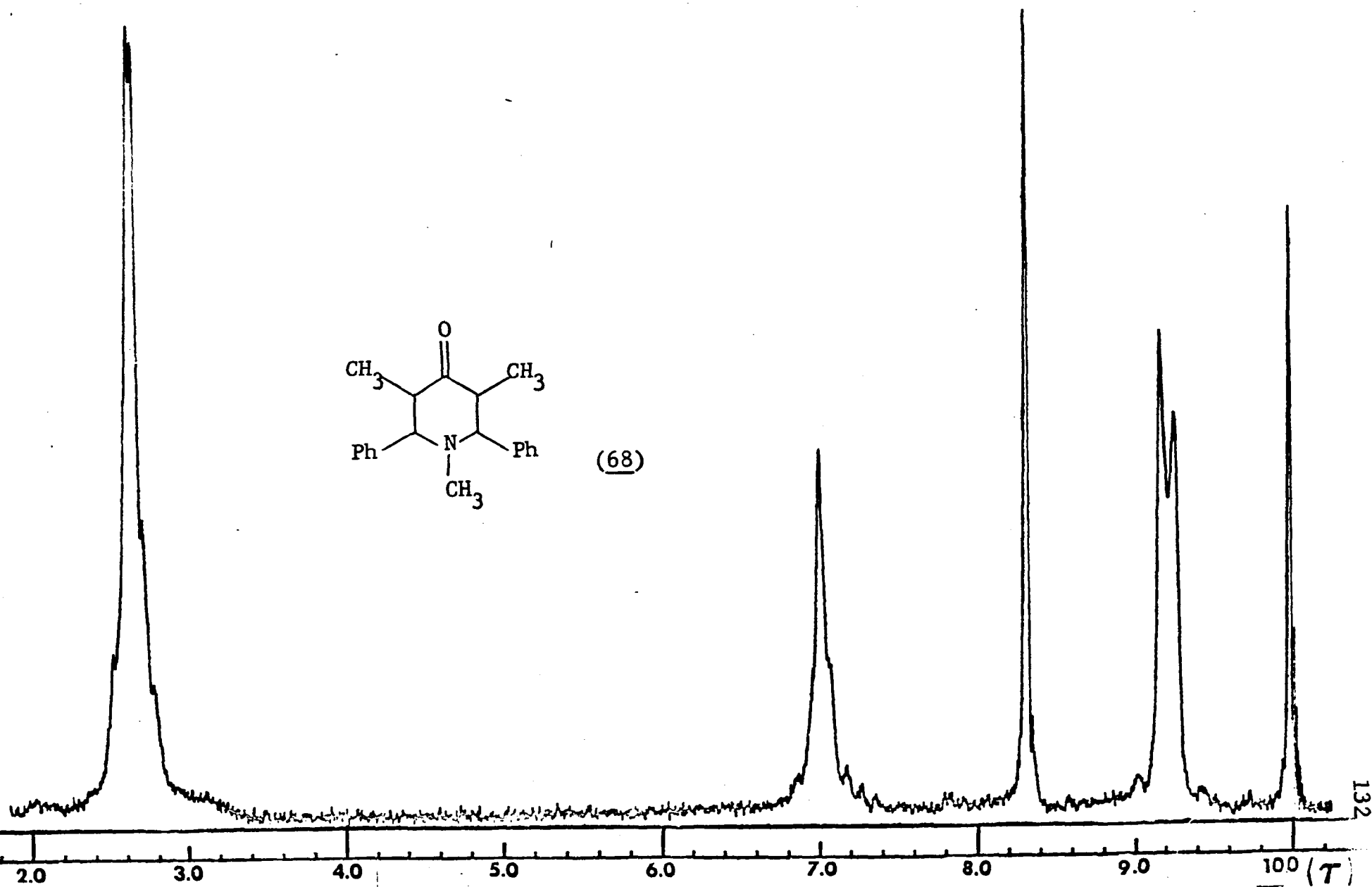
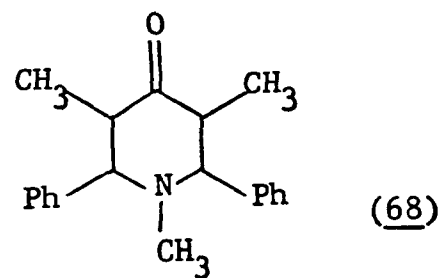
Curve J



(67)



Curve K





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"Conformational Studies with 3-Piperidinols", with R. E. Lyle, Abstracts, 153rd National Meeting of The American Chemical Society, Miami Beach, Florida, April 1967, p. 93-0.

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